Endocrine Abstracts

May 2015 Volume 37
ISSN 1479-6848 (online)

17th European Congress of Endocrinology 2015

16–20 May 2015, Dublin, Ireland

published by
bioscientifica

Online version available at
www.endocrine-abstracts.org

Endocrine Abstracts

Volume 37
May 2015

17th European Congress of Endocrinology

16–20 May 2015, Dublin, Ireland

EDITORS

The abstracts were marked by the Abstract Marking Panel selected by the Programme Organising Committee

ECE 2015 Programme Organising Committee

W Arlt Chair
J Visser Co-chair
F Beuschlein Co-chair

Members

P Beck-Peccoz
P Burman
J Christiansen
M Hewison
I Huhtaniemi
E Husebye
M Korbonits
M Laan
E Lalli
D Marks
J Mittag
M Niedziela
N Pitteloud
M Pfeifer
JA Romijn
R Ross
D Schulte
R Semple
M Sherlock
A Spada
M Tena-Sempere
C Thompson

Abstract Marking Panel

A Agha Ireland
M Alevizaki Greece
B Allolio Germany
J Argente Spain
G Assié France
S Babajko France
K Badenhoop Germany
D Bassett UK
E Baudin France
A Beckers Belgium
A Berruti Italy
J Bertherat France
B Bilinska Poland
M Bluher Germany
K Boelaert UK
A Boelen The Netherlands
R Bouillon Belgium
J-P Bourguignon Belgium
M L Brandi Italy
K Briot France
G Brunetti Italy
C Buchanan UK
J S Carroll UK
J Castano Spain
K Chatterjee UK
B Chini Italy
I Chiodini Italy
J Chowen Spain
T Coll UK
C Daousi UK
W de Herder Netherlands
E de Koning The Netherlands
R de Krijger The Netherlands
W Dhillo UK
G Di Dalmazi Germany
E Diamanti-Kandarakis Greece
F Dotta Italy
J Drouin Canada
L Duntas Greece
G Eisenhofer Germany
F Fallo Italy
P Farahani Canada
S Farooqi UK
M Fassnacht Germany
R Feelders The Netherlands
U Feldt-Rasmussen Denmark
F Flamant France
E Fliers The Netherlands
C Fluck Switzerland
S Franks UK
W Fraser UK
J Frystyk Denmark
R Gä'rtner Germany
A Gimenez-Roqueplo Spain
J Gomez-Ambrosi Spain
R Granata Italy
J Gromoll Germany
A Grossman UK
S Hahner Germany
R Hampl Czech Republic
S Herzig Germany
A Hoeflich Germany
C Hofig Sweden
J Hofland Netherlands
W Högler UK
P Igaz Hungary
S Inzucchi USA
E R Isenovic Serbia
M-L Jaffrain-Rea Italy
J Janssen Netherlands
C Jazdzewski Poland
D Jezova Slovakia
N Jørgensen Denmark
J Jürimäe Estonia
A Juul Denmark
A Kalsbeek Netherlands
G Kaltsas Greece
A Karlsson Sweden
F Kelestimur Turkey
R Kineman USA
H Krude Germany
J Laven The Netherlands
G Lavery UK
P Lips Netherlands
A Luger Austria
R M Luque Spain
M Maggi Italy
J Magre France
M Mannelli Italy
F Mantero Italy
C McCabe UK
R Mitchell UK
E Nagy Hungary
J Newell-Prize UK
K Owen UK
M Paez-Pereda Germany
J J Palvimo Finland
S Papopolous Netherlands
S Pearce UK
R Peeters The Netherlands
P Perros UK
L Persani Italy
M Pfeifer Slovenia
M Poutanen Finland
D Power Portugal
V Prevot France
S Radian UK
E Rajpert-De Meyts Denmark
M Reincke Germany
S Rice UK
M Robledo Spain
P Rodien France
C Ronchi Italy
R Ross UK
G P Rossi Italy
M Ruchala Poland
M Sahin Turkey
D Salvatore Italy
S Sanlioglu Turkey
P Saunders UK
M Schiffer Germany
S Schmid Germany
P Schöffski Belgium
J Schopohl Germany
M Schott Germany
R Sharpe UK
M Simoni Italy
J Smit The Netherlands
U Smith Sweden
E Stener-Victorin Sweden
M Terzolo Italy
M Theodoropoulou Germany
P Thompson UK
V Tillmann Estonia
H Timmers The Netherlands
J Tomlinson UK
J Toppari Finland
Z Toth Hungary
S Tsagarakis Greece
M Tzanela Greece
E Valassi Spain
A J van der Lelij Netherlands
W van Hul Belgium
L van Rossum Netherlands
V Volke Estonia
R Voutilainen Finland
I Wilkinson UK
T Williams Italy
Z Wu Germany
J Young France
M Zatelli Italy
M Zennaro France

SPONSORS

The ESE would like to thank its Corporate Members and the ECE 2015 sponsors

ECE Corporate Members

Eli Lilly
Ipsen
Laboratoire HRA Pharma
Merck Serono (MSD)
Novartis Pharmacueticals
Novo Nordisk
Pfizer
Sandoz International Gmbh
ViroPharma SPRL

Gold Sponsors

Ipsen
Novartis Pharmaceuticals

Bronze Sponsors

MSD International GmbH

ESE Office
Euro House
22 Apex Court
Woodlands
Bradley Stoke
Bristol BS32 4JT, UK

Contact: Andrea Davis
Tel: +44 (0)1454 642247
Fax: +44 (0)1454 642222
E-mail: info@euro-endo.org
Web site: www.ese-hormones.org

ECE 2015 Secretariat
Bioscientifica Ltd
Euro House, 22 Apex Court
Woodlands
Bradley Stoke
Bristol BS32 4JT, UK

Contact: Claire Arrigoni
Tel: +44 (0)1454 642240
Fax: +44 (0)1454 642222
E-mail: conferences@bioscientifica.com
Website: http://www.bioscientifica.com

CONTENTS

17th European Congress of Endocrinology 2015

PRIZE LECTURES AND BIOGRAPHICAL NOTES

PLENARY LECTURES

SYMPOSIA

EPOSTER PRESENTATIONS

INDEX OF AUTHORS

Prize Lectures and Biographical notes

European Journal of Endocrinology Prize Winner

The *European Journal of Endocrinology* Prize is awarded to a candidate who has contributed significantly to the advancement of the knowledge in the field of endocrinology through publication. Further information on the prize can be found at http://www.ese-hormones.org/prizes/eje.aspx. This year's recipient is Dr Robert Semple. The prize will be presented as part of the ECE 2015 opening ceremony where Dr Semple will deliver his lecture. Dr Semple will also write a review article based on this lecture to be published in the *European Journal of Endocrinology*.

Robert Semple, University of Cambridge, UK

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

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

Dr Semple is also a fellow of Clare College, Cambridge, and Director of the Cambridge MB PhD programme.

The *European Journal of Endocrinology* Prize Lecture

Insulin Action in Common Disease: Too Much, Too Little, or Both?

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

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

Geoffrey Harris Prize Winner UK

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

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

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

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

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

The Geoffrey Harris Prize Lecture

Understanding energy sensors, understanding neuroendocrine function

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

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

Work carry out by different groups have uncovered the mechanism by which hypothalamic neurons sense nutrient bioavailability, with a relevant contribution of AMPK and mTOR among others, as sensors of cellular energy status. Interestingly, the orexigenic/anorexigenci effects of different neuropeptides and peripheral hormones appear to be mediated by an AMPK-driven regulation of hypothalamic lipid metabolism, and may involve also the modulation of mTOR signaling. Their integrative role in terms of energy homeostasis involved different mechanisms including regulation of food intake, energy expenditure or metabolic homeostasis at relevant target tissues. Furthermore recent developments has shown the involvement of central energy sensors in orchestrating the adaptative response of different hypothalamic-pituitary axis to changes in energy availability. This development helps to understand the interplay between peripheral signals and central neurotransmitters and neuropeptides in order to elicit a biological response at the whole organism.

Plenary Lectures

PI 3-Kinase: connecting diabetes, obesity and cancer
PL1

Abstract unavailable.

DOI: 10.1530/endoabs.37.PL1

European Hormone Medal Lecture: Obesity and insulin resistance: Lessons from human genetics
PL2

Abstract unavailable.

DOI: 10.1530/endoabs.37.PL2

The genomics of adrenocortical tumors
PL3

Abstract unavailable.

DOI: 10.1530/endoabs.37.PL3

Congenital Adrenal Hyperplasia (CAH): Mechanisms and management across the life span
PL4

Overhauling the pathophysiology and treatment of congenital adrenal hyperplasia across the lifetime

Richard Auchus
University of Michigan, Ann Arbor, Michigan, USA.

The most common form of congenital adrenal hyperplasia is 21-hydroxylase deficiency (21OHD). The treatment for classic (severe) 21OHD differs from treatment of most other types of adrenal insufficiency in that not only must one replace the glucocorticoid and mineralocorticoid deficiency but also attenuate the high adrenal-derived androgen production. In order to reduce the adrenocorticotropin (ACTH) driven androgen production, supraphysiologic doses of glucocorticoid and/or long-acting synthetic glucocorticoids are often used, to compensate for the short half-life of oral hydrocortisone. In particular, the early morning rise in ACTH and adrenal steroids is difficult to manage in 21OHD. Consequently, adults with 21OHD suffer from high rates of obesity, low bone density, and cushingoid features.
Several strategies have been employed recently to improve the control of androgen excess in 21OHD while limiting the dose of glucocorticoid to the physiologic replacement range. Modified-release forms of hydrocortisone have been developed to prolong its half-life, and hydrocortisone has been delivered via a continuous subcutaneous infusion system, to match the dosage and timing to the clinical need. Abiraterone acetate, the prodrug for the potent 17-hydroxylase/17,20-lyase (CYP17A1) inhibitor abiraterone, markedly lowered androgens in six adult women with 21OHD in a short-term study of 100–250 mg/day. The non-steroidal antagonist of the corticotropin-releasing factor receptor type 1 (CRFR1), NBI-77860, lowered ACTH and 17OHP in eight adult women with 21OHD. These therapies are all under further study to determine safety and efficacy in children and adults.
In addition, the pathways of androgen excess in 21OHD have been unclear, and the best biomarkers for diagnosis and titration of therapy are debated. Recent work suggests that the alternate or 'backdoor' pathway to dihydrotestosterone via 5α-reduced precursors significantly contributes to the androgen excess of infants with 21OHD. Specific 21- and 19-carbon steroids of adrenal origin might be better biomarkers of 21OHD than 17-hydroxyprogesterone and testosterone.

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

DOI: 10.1530/endoabs.37.PL4

Insulin signalling and action
PL5

Interplay between genes and environment in insulin resistance and metabolic syndrome: the unique role of the gut microbiome

C Ronald Kahn, Siegfried Ussar & Shiho Fujisaka
Joslin Diabetes Center, Boston, Massachusetts, USA.

Both type 2 diabetes (T2D) and obesity are the result of a complex interaction between genes and environment, as well as complex interactions between the tissues of the body. The latter include effects of new adipokines released by fat that influence insulin action in other tissues of the body, as well as increasingly complex effects of the brain and adipose tissue on control of metabolism. Mouse models provide a powerful tool to investigate these interactions in disease pathogenesis. These studies have revealed new classes of insulin action and new mechanisms of tissue cross-talk in the pathogenesis of obesity and diabetes, as well as impact of genes, environment and the gut microbiome on disease pathogenesis. For example, we have previously shown that C57BL/6 mice (B6J) are susceptible to diet induced obesity, marked insulin resistance and metabolic syndrome, while 129S1 mice from Jax (here identified as 129J) are resistant to development of obesity and metabolic syndrome. Likewise, when challenged with genetically-induced insulin resistance, more than 90% of B6J mice develop diabetes, while $<5\%$ of 129J mice become diabetic. Genome-wide scanning indicates at least one of the genes involved in the difference in insulin resistance is the gene for PKCδ. Recently, we have extended this interaction between genes and environment using a unique experimental paradigm in which we have compared the responses of these two strains of mice from Jax to an almost isogenic strain of 129 mice from Taconic Farms (129T). Interestingly, while the 129J mice are resistant to this high fat diet challenge, 129T mice show a different phenotype, being susceptible to diet-induced obesity, but retaining normal insulin sensitivity. Thus, compared to B6J mice, the 129T mice represent a model of the 'healthy' obese. This phenotype however is related to environmental influences. Following 'normalization' of the environment by inbreeding these three strains of mice in our animal facility for several generations, the 129T mice lose their susceptibility to diet-induced obesity and became very similar to the obesity resistant 129J mice. Analysis of the composition of gut microbiota reveals profound differences in the relative amounts of bacterial species in the intestine between the three different commercial mouse lines and their environmentally-conditioned equivalents. The composition of the microbiome for each strain uniquely correlate with the genetic background, different diets and different environmental histories, i.e. the provenance, of these mice. These changes in microbiota are also associated with changes in production of the inflammatory mediators by the gut and to the production and secretion of gut hormones known to influence energy intake and metabolic homeostasis. When mice are treated with different antibiotics, the microbiome changes and this is associated with changes in insulin signaling and metabolism. Our study allowed us for the first time to unravel how diet, genetic background, as well as original housing conditions, each independently contribute in shaping the gut flora composition which will drive the susceptibility of mice to diet-induced obesity, which can be reprogrammed by exposing mice to new environmental factors.

Disclosure
NIH: R01 DK055545; NIH: R01 DK031036; NIH: P30 DK036836.

DOI: 10.1530/endoabs.37.PL5

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

PL6

Abstract unavailable.

DOI: 10.1530/endoabs.37.PL6

Obesity and the skeleton

PL7

Obesity and the skeleton

Juliet Compston
Cambridge Biomedical Campus, Cambridge, UK.

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

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

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

DOI: 10.1530/endoabs.37.PL7

From base change to better care in diabetes

PL8

Abstract unavailable.

DOI: 10.1530/endoabs.37.PL8

Symposia

Glucocorticoid action in health and disease

S1.1

Dietary regulation of cortisol production and metabolism in humans

Brian R Walker
University of Edinburgh, Scotland, UK.

The hypothalamic-pituitary adrenal (HPA) axis plays a key role in the metabolic response to stress, so it is to be anticipated that cortisol signalling might in turn be regulated by nutritional status. This regulation might operate either centrally, controlling ACTH and hence plasma cortisol, or peripherally, controlling metabolism of cortisol in target tissues.
Plasma cortisol levels are elevated during starvation in animals and a recent meta-analysis confirms that starvation elevates plasma cortisol also in humans, although the effect may be transient. Cortisol levels also rise transiently after meals in humans. It is usually assumed that these effects of starvation and feeding are mediated by central alterations in the HPA axis. However, using stable isotope steroid tracers and test meals with different macronutrient components, we demonstrated that enhanced peripheral regeneration of cortisol contributes substantially to the rise in plasma cortisol after consumption of carbohydrate but not fat. We further demonstrated acute up-regulation of 11β-HSD1 activity *in vivo* by insulin but not lipid infusions.
With chronic dietary manipulation in humans, however, a low carbohydrate diet induces up-regulation of 11β-HSD1, an effect which is mimicked by metformin administration, suggesting that hyperinsulinaemia may chronically down-regulate 11β-HSD1. Indeed, in obesity without diabetes 11β-HSD1 is down-regulated in liver. However, other factors may come into play in obesity, particularly up-regulation of adipose 11β-HSD1 induced by intra-adipose inflammation. A complex regulation of 11β-HSD1 by pathways involved in nutrient signalling appears to be species- and tissue-specific, e.g. Tith changes induced by PPAR agonists and growth hormone in mice not readily recapitulated in humans.
We conclude that both the HPA axis and peripheral regeneration of cortisol are influenced by nutritional status and dietary macronutrient content. Variations in glucocorticoid signalling may therefore contribute to adverse effects not only of total calorie excess, but also specific dietary components.
Disclosure
British Heart Foundation.

DOI: 10.1530/endoabs.37.S1.1

S1.2

Subclinical Cushing's syndrome and cardiovascular disease

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

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

DOI: 10.1530/endoabs.37.S1.2

S1.3

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

Alex Odermatt
University of Basel, Basel, Switzerland.

11β-hydoxysteroid dehydrogenase type 1 (11β-HSD1) essentially catalyzes the conversion of the inactive endogenous glucocorticoid cortisone (11-dehydro-corticosterone in rodents) and the synthetic prednisone into the active cortisol (corticosterone in rodents) and prednisolone. The association of an elevated expression of 11β-HSD1 with metabolic disease has been extensively studied in humans and in rodent models. It is generally assumed that the effects that are observed upon modulating 11β-HSD1 function by pharmacological inhibition or genetic manipulation in transgene mouse models are glucocorticoid-dependent. However, 11β-HSD1 is a multi-functional carbonyl reductase involved in the hepatic metabolism of various non-steroidal xenobiotics. Besides, it has a role in the metabolism of neurosteroids, oxidized cholesterol and bile acids. In as much these alternative substrates might affect 11β-HSD1-dependent glucocorticoid activation can, so far, only be estimated from *in vitro* studies, and further investigations *in vivo* are needed.
A recent study in 11β-HSD1 deficient mice revealed elevated concentrations of circulating free bile acids, an effect that was more pronounced in global than liver-specific knockout mice. A reduced expression of the bile acid coenzyme A ligase Fatp5 suggested an impaired bile acid amidation and subsequently decreased conjugation. These effects of the lack of 11β-HSD1 activity seem to be glucocorticoid-independent because intra-hepatic corticosterone levels and glucocorticoid receptor target gene expression were not decreased in livers from liver-specific knockout mice. Furthermore, Fatp5 expression was not altered in mice deficient in hepatic glucocorticoid receptors.
Thus, the elucidation of glucocorticoid-independent functions of 11β-HSD1, such as its role in oxysterol and bile acid homeostasis, and the relevance for metabolic and immune disorders warrants further investigations.

DOI: 10.1530/endoabs.37.S1.3

Management of type 2 diabetes: State of the art

S2.1

Blood pressure management in Type 2 Diabetes Mellitus

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

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

DOI: 10.1530/endoabs.37.S2.1

S2.2

Blood glucose management

Kåre Birkeland
Oslo University Hospital, Oslo, Norway.

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

DOI: 10.1530/endoabs.37.S2.2

S2.3

PCSK9 antibodies for the treatment of hypercholesterolemia

Ioanna Gouni-Berthold
University of Cologne, Cologne, Germany.

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

DOI: 10.1530/endoabs.37.S2.3

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

S3.1

TBI: whom to screen for hypopituitarism

Mark Hannon[1,2]
[1]St. Bartholomew's Hospital, London, UK; [2]Beaumont Hospital, Dublin, Ireland.

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

DOI: 10.1530/endoabs.37.S3.1

S3.2

Genetic causes of hypopituitarism

Thierry Brue[1,2]
[1]Aix-Marseille University, CNRS, CRN2M UMR 7286, Marseille, France; [2]Service d'Endocrinologie, Hôpital de la Conception, APHM, Marseille, France.

Genetic causes of anterior pituitary hormone deficiencies may result in combined or isolated pituitary hormone deficiencies. These disorders represent a heterogeneous group of rare diseases leading to defective function of specific pituitary cell types. Since the first description of POU1F1 human mutations, several other genetic defects of transcription factors have been reported with variable degrees of phenotype-genotype correlations. However to date, despite the identification of a growing number of genetic causes of isolated or multiple pituitary deficiencies, the etiology of most (80–90%) congenital cases of hypopituitarism remains unsolved. Identifying new etiologies is of importance as a post-natal diagnosis to better diagnose and treat the patients (delayed pituitary deficiencies, differential diagnosis of a pituitary mass on MRI…), and as a prenatal diagnosis to decrease the risk of early death (undiagnosed corticotroph deficiency for instance).
Some patients harbour a complex phenotype including anterior pituitary hormone deficiencies in association with extra pituitary abnormalities or malformations on MRI such as pituitary stalk interruption syndrome or midline defects. The transcription factors genes involved in these phenotypes (for instance LHX3, LHX4) are early expressed in regions that determine the formation of forebrain and related midline structures such as the hypothalamus and pituitary. Mutations in these genes are therefore characterized by marked phenotypic heterogeneity. Among more recently identified forms, the DAVID syndrome, an association of a deficit in adrenocorticotrophin with recurrent infections due to variable immunodeficiency was recently associated with NFKB2 mutations. In contrast, 'pure' endocrine phenotypes include anterior pituitary hormone deficiencies (progressive or not) with normal hypothalamo-pituitary morphology at MRI (regardless of the size of the pituitary gland) and no extra pituitary malformation. They are due to mutations of late-acting pituitary specific transcription factors. In such a context, PROP1 gene mutations remain the most frequently reported genetic defect.

DOI: 10.1530/endoabs.37.S3.2

S3.3

Drug induced hypopituitarism

Salvatore Maria Corsello
Catholic University School of Medicine, Rome, Italy.

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

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

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

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

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

DOI: 10.1530/endoabs.37.S3.3

Thyroid hormone and cardiovascular system

S4.1

Subclinical hypothyroidism and cardiovascular consequences in childhood

Mariacarolina Salerno
Department of Translational Medical Sciences, University Federico II, Naples, Italy.

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

In adults with SH a pattern of CV abnormalities (dyslipidemia, insulin resistance, endothelial and diastolic dysfunction) has been observed even in mild SH cases with TSH between 4.5 and 10 mU/L.

However, a positive effect of levo-thyroxine (L-T_4) therapy on CV morbidity and survival rates has not been clearly demonstrated although there are some evidence indicating an improvement in the lipid profile and left ventricular function.

It is well known that risk factors accelerating the development of atherosclerotic disease begins in childhood and may be predictive of CV risk in adulthood. Whether SH in children predisposes to adverse CV outcomes in adulthood is still unclear. Data on children are scanty and most of the studies are limited by the small number and the heterogeneity of the populations studied and by the presence of several confounding factors, as obesity and autoimmunity, making the evaluation of the direct impact of SH on CV risk difficult.

Recent data from a selected population of subjects with mild long-lasting idiopathic SH suggested that untreated SH children may develop a cluster of subtle metabolic abnormalities as increased abdominal adiposity and slight alterations in lipid profile and homocysteine levels. The clinical significance of these changes as early steps in initiation of atherogenesis is difficult to establish. Therefore, although further studies evaluating the long-term CV consequences of childhood-onset SH and the effect of L-T_4 therapy are still to be made, the evidences available suggest that these children should be carefully monitored for metabolic complications that may expose them to an higher risk of future CV diseases.

DOI: 10.1530/endoabs.37.S4.1

S4.2

Cardiovascular impact of thyroid hormone receptor mutations

Krishna Chatterjee
Institute of Metabolic Science, University of Cambridge, Cambridge, UK.

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

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

Recognised more recently, features of Resistance to Thyroid Hormone due to defective TRα (RTHα) include growth retardation, neurodevelopmental delay, skeletal dysplasia and constipation, but with near-normal thyroid function tests. The cardiovascular manifestations of this disorder include bradycardia and lower blood pressure; following thyroxine therapy, changes in these parameters and cardiac indices are blunted, reflecting myocardial resistance to hormone action.

The divergent phenotypes of RTHβ and RTHα highlight the relative importance of α and β receptor subtypes in mediating TH action in myocardium and other tissues.

DOI: 10.1530/endoabs.37.S4.2

S4.3

Cardiovascular actions of novel Thyroid Hormone metabolites

Carolin Höfig
Karolinska Institutet, Stockholm, Sweden.

Thyroid hormone (TH) is one of the key players in modulating cardiovascular function. The hormone increases heart rate and force of contraction by modulating cardiac gene expression, thereby providing a molecular explanation for the clinical correlation between hyperthyroidism and cardiovascular mortality. The talk will present current aspects of cardiovascular function mediated by newly discovered TH metabolites. Recent studies have shown that a single injection of 3-iodo-L-thyronamine (3-T1AM), a decarboxylated and deiodinated TH derivative, leads to rapid decreases in heart rate and cardiac output. Although 3-T1AM is rapidly converted to several metabolites *in vivo*, the strong acute pharmacological responses of bradycardia and negative inotropy were solely attributed to 3-T1AM, leaving potential contributions of downstream products untested (e.g. 3-iodothyroacetic (TA1) acid or N-acetyl-3-T1AM (NAc-3-T1AM). Our studies revealed that TA1, the main degradation product of 3-T1AM, lacks any cardiovascular effects in mice, and thus constitutes an important inactivation product of 3-T1AM. However, NAc-3-T1AM, which is produced in liver and WAT from 3-T1AM, significantly increases heart rate and blood pressure in mice and directly enhances contractility of primary cardiomyocytes. Both effects are blocked by the β-adrenergic antagonist timolol maleate, demonstrating that the actions of NAc-3-T1AM on cardiomyocytes require β-adrenergic receptors. Based on our findings, we identify NAc-3-T1AM as a unique endocrine TH metabolite, providing a previously unknown link between liver, WAT and cardiovascular function.

Disclosure
This work is supported by grants from the Deutsche Forschungsgemeinschaft (HO 5096/1-1), the Karolinska Institutet's Foundation, the Swedish Research Council and Hjärt-och Lungfonden.

DOI: 10.1530/endoabs.37.S4.3

Endocrinology of ageing men

S5.1

Abstract unavailable.

DOI: 10.1530/endoabs.37.S5.1

S5.2

Osteoporosis in ageing men

Dirk Vanderschueren
KU Leuven, leuven, Belgium.

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

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

DOI: 10.1530/endoabs.37.S5.2

S5.3

Abstract unavailable.

DOI: 10.1530/endoabs.37.S5.3

Beyond Phosphorus: multiple actions of FGF23

S6.1

FGF23: a cornerstone of phosphate/calcium metabolism

Justine Bacchetta[1,2]
[1]Paediatric Nephrology, Bron, France; [2]INSERM 1033 LYOS, Lyon, France.

Since its first description as a phosphaturic agent in the early 2000s, the Fibroblast Growth Factor 23 (FGF23) has rapidly become the third key player of phosphate/calcium metabolism with the two 'old' PTH and vitamin D.

FGF23 is a protein synthesized by osteocytes that has three main effects: hypophosphatemia (through an inhibition of phosphate reabsorption in the proximal tubule), decreased PTH levels and decreased 1–25 OH_2 levels (through an inhibition of 1α hydroxylase and an activation of 24 hydroxylase activity in the kidney). Off-targets of FGF23 have also been demonstrated, notably on cardiomyocytes and monocytes. The links between iron metabolism and FGF23 on one hand, and between FGF23 and bone mineralization on the other hand, seem also of importance, although still under investigation. The single-pass transmembrane Klotho protein, an anti-aging protein, is required *in vivo* for FGF23-mediated receptor activation, at least for its renal effects.

In human diseases, FGF23 can be deregulated, either in genetic diseases, either in acquired diseases. Four groups can be distinguished: diseases with primary increase of FGF23 levels (e.g., hypophosphatemic rickets or tumor-induced osteomalacia), diseases with primary decrease of FGF23 levels (e.g., hyperphosphosphatemic tumoral calcinosis), diseases with secondary increase of FGF23 levels (e.g., chronic kidney disease, CKD), and diseases with secondary decrease of FGF23 levels (e.g., VDR deficiency leading to vitamin D-resistant rickets).

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

DOI: 10.1530/endoabs.37.S6.1

S6.2

Target cell responses to FGF23

Reinhold Erben
University of Veterinary Medicine Vienna, Vienna, Austria.

Fibroblast growth factor-23 (FGF23) FGF23 is a bone-derived hormone which down-regulates renal proximal tubular phosphate reuptake and 1α-hydroxylase expression, the key enzyme for production of the vitamin D hormone, 1α, 25-dihydroxyvitamin D_3 ($1.25(OH)_2D$). The molecular mechanism of the phosphaturic action of FGF23 has recently been elucidated. FGF23 directly downregulates membrane expression of the sodium-phosphate cotransporter NaPi-2a in proximal tubular epithelium by serine phosphorylation of the scaffolding protein Na^+/H^+ exchange regulatory cofactor (NHERF)-1 through FGF receptor-αKlotho complex-mediated activation of extracellular signal-regulated kinase 1 and 2 (ERK1/2) and serum/glucocorticoid-regulated kinase-1 (SGK1). However, FGF23 not only targets renal proximal tubular cells, but also has distinct effects on the distal nephron, in bone, and possibly in the heart and in blood vessels. In renal distal tubules, FGF23 stimulates apical membrane abundance of TRPV5 and renal calcium reabsorption in a αKlotho dependent manner through a signaling cascade involving ERK1/2, SGK1, and with-no-lysine kinase-4 (WNK4). Because activation of WNK4 not only upregulates membrane transport of TRPV5 but also of the sodium-chloride co-transporter NCC, FGF23 also increases sodium reabsorption in distal renal tubules. Recent experimental evidence suggests that the calcium- and sodium-conserving function of FGF23 may be of pivotal importance in the pathophysiology of chronic kidney disease. In bone, we identified FGF23 as a strong transcriptional suppressor of alkaline phosphatase in osteoblastic cells, acting through FGF receptor-3 in a Klotho independent manner. Hence, FGF23 secreted from osteocytes may form an autocrine/paracrine feedback loop for the local fine-tuning of bone mineralization. Taken together, there is emerging evidence that FGF23 is not only a phosphaturic and vitamin D-regulating hormone, but rather a pleiotropic hormone with additional direct effects on calcium homeostasis, sodium homeostasis, blood pressure regulation, and bone mineralization.

Disclosure
Austrian Science Fund FWF P 24186-B21.
DOI: 10.1530/endoabs.37.S6.2

S6.3

Novel actions of FGF23

Myles Wolf
Northwestern University, Chicago, IL, USA.

The discovery that mutations in fibroblast growth factor 23 (FGF23) cause autosomal dominant hypophosphatemic rickets transformed our understanding of phosphate homeostasis in health and disease (White *et al. Nat Genet* 2000). Since then, the critical role of FGF23 in mineral metabolism in chronic kidney disease has been established (Larsson *et al. Kidney Int* 2003; Gutierrez *et al. J Am Soc Nephrol* 2005). Elevated FGF23 has emerged as the earliest alteration of disordered mineral metabolism in chronic kidney disease (Isakova *et al. Kidney Int* 2011). Several studies now demonstrate that elevated FGF23 is also a novel biomarker of risk for CKD progression, adverse cardiovascular outcomes and death among patients with chronic kidney disease (Fliser *et al. J Am Soc Nephrol* 2007; Gutierrez *et al. N Engl J Med* 2008; Isakova *et al. JAMA* 2011; Kendrick *et al. J Am Soc Nephrol* 2011; Jean *et al. Nephrol Dial Transplant* 2009). More recently, FGF23 was demonstrated to contribute mechanistically to development of left ventricular hypertrophy, which may underlie an important component of the association of elevated FGF23 levels with high risk of cardiovascular events (Faul *et al. J Clin Invest* 2011; Scialla *et al. J Am Soc Nephrol* 2013). These studies elevated FGF23 and disordered phosphate homeostasis from powerful

biomarker to novel mechanism of cardiovascular disease in chronic kidney disease. This session will describe the latest data on FGF23 in chronic kidney disease with specific emphasis on the role of FGF23 in cardiovascular disease.

DOI: 10.1530/endoabs.37.S6.3

Novel mechanisms of central weight regulation

S7.1

Nutritional regulation of hypothalamic inflammation

Julie A Chowen[1,2]
[1]Department of Endocrinology, Hospital Infantil Universitario Niño Jesús, Madrid, Spain; [2]CIBERobn, Instituto Carlos III, Madrid, Spain.

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

Disclosure
This work was funded by grants from Fondos de Investigación Sanitaria (PI100747; PI1302195), Ministerio de Ciencia e Innovación (BFU2011–27492), Centro de Investigación Biomédica en Red Fisiopatología de Obesidad y Nutrición (CIBEROBN), Instituto Carlos III, Madrid, Spain.

DOI: 10.1530/endoabs.37.S7.1

S7.2

Regulation of hypothalamic development by maternal nutrition

Merly Vogt[1], Lars Paeger[2], Simon Hess[2], Sophie Steculorum[1], Susanne Neupert[2], Reinhard Predel[2], Peter Kloppenburg[2], Tamas Horvath[3] & Jens Brüning[1]
[1]MPI for Metabolism Research, Cologne, Germany; [2]Biocenter, Institute for Zoology, University of Cologne, Cologne, Germany; [3]Program in Integrative Cell Signaling and Neurobiology of Metabolism, Section of Comparative Medicine, Department of Obstetrics/Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT, USA.

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

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

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

DOI: 10.1530/endoabs.37.S7.2

S7.3

Hypothalamic tanycytes in metabolic regulation

Vincent Prevot
Inserm U1172, University of Lille, Lille, France.

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

DOI: 10.1530/endoabs.S7.3

The endocrine gut (*Endorsed by Endocrine Connections*)

S8.1

Gut microbiota and incretins

Patrice D Cani[1,2]
[1]Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium; [2]Walloon Excellence in Life sciences and BIO Technology, Brussels, Belgium.

The distal gut harbours microbial communities that outnumber our own eukaryotic cells. Over the last 15 years, our work has been devoted to examine the way by which gut microbiota interacts with nutrients and host physiology. We and others have suggested that cross-talks between gut microbiota and the host cells contribute to the regulation of energy, glucose and lipid homeostasis.

We described the concept of metabolic endotoxemia (increase in plasma LPS levels) as one of the triggering factors leading to the development of the metabolic inflammation and insulin resistance. Following this discovery, we found that the major factor involved in the development of metabolic endotoxemia observed upon obesity is related to the gut barrier function.

Bacterial metabolism of nutrients in the gut is able to drive the release of bioactive compounds (including short-chain fatty acids or lipid metabolites), which interact with host cellular targets to control energy metabolism and immunity.

We found in both rodents and humans that prebiotics, administration changed gut microbiota composition and activity.

In rodents, we found that specific change in the gut microbiota composition improves glucose tolerance, *via* GLP-1 dependent mechanisms and gut barrier *via* GLP-2 dependent mechanisms. More specifically, we found that prebiotics increased L-cells number and associated parameters (intestinal proglucagon mRNA expression, plasma GLP-1 and 2 levels).

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

This work is supported by ERC Starting Grant ENIGMO 336452.
Disclosure
ERC Starting Grant ENIGMO 336452.

DOI: 10.1530/endoabs.S8.1

S8.2

Abstract unavailable.

DOI: 10.1530/endoabs.37.S8.2

S8.3

Stimulation of incretin secreting cells

Frank Reimann
University of Cambridge, Cambridge, UK.

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

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

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

DOI: 10.1530/endoabs.37.S8.3

Steroid hormone action in target tissues

S9.1

Tissue-specific sex steroid action: role of HSD17B-enzymes

Matti Poutanen
Institute of Biomedicine, University of Turku, Turku, Finland.

Recent data from us and others have evidently shown that steroid metabolism at the target tissues is a key determinant regulating the availability of high affinity ligands for steroid receptors. Thus, the serum concentrations of the steroids do not necessary mimic their target tissue concentrations in several physiological and pathophysiological settings. Accordingly, among the other steroid metabolizing enzymes, the expression of hydroxysteroid dehydrogenase- (HSD17B) enzymes catalyzing the conversion between 17-keto and 17-hydroxysteroids are expressed in various sex steroid target tissues. So far, among the various HSD17B enzymes the expression of HSD17B1, HSD17B2, HSD17B3, HSD17B5 (AKR1C3) and HSD17B6 has shown the strongest association with steroid metabolism in both preclinical models and clinical specimens. HSD17B1 and HSD17B2 enzymes are the ones with the strongest association with altered estrogen metabolism, and are, for example, differentially expressed in endometriosis lesions and in the eutopic endometrium. This results into an altered estradiol/estrone balance in the endometriosis, being one of the mechanisms promoting the growth of the lesions. Role of HSD17B1 in the activation of the sex steroids is also supported by multiple phenotypic alterations in the transgenic mice expressing the human HSD17B1, as well as by the data obtained in the HSD17B1 knockout (KO) mice. Similarly to that of endometriosis, novel routes for the local sex steroid synthesis in the castration resistant prostate cancer have been identified, and the strong intra-tumor androgen production is associated with up-regulation of HSD17B5 and HSD17B6 expression. However, especially the phenotypes of the KO mouse models have predicted also other metabolic roles for several other HSD17B enzymes, and thus, a critical evaluation of physiological role of all HSD17B-enzymes *in vivo* is essential. For example, HSD17B7 KO mice showed a role for the enzyme in cholesterol synthesis, and HSD17B12 and HSD17B13 KO mice indicated a role of the enzymes in lipid metabolism. In conclusion, novel HSD17B-enzyme dependent pathways for sex steroid synthesis and metabolism are emerging at target tissues, and provides new possibilities for the treatment of sex steroid-dependent diseases by HSD17B-inhibitors.

Disclosure
Academy of Finland, Tekes: Finnish Funding Agency for Innovation, European Regional Development Fund, Novo Nordisk Foundation, The Finnish Cancer Organisations.

DOI: 10.1530/endoabs.37.S9.1

S9.2

Steroid sulphatase and colon cancer

Paul Foster
University of Birmingham, Birmingha, West Midlands, UK.

Although not normally considered an oestrogen responsive tissue, compelling evidence now exists suggesting that the colon is responsive to oestrogenic effects. Results from the Women's Health Initiative demonstrated that post-menopausal women taking oestrogen and progestins as hormone-replacement therapy (HRT) had a 40% reduction in developing colorectal cancer (CRC). Intriguingly, patients taking oestrogen supplements at the time of CRC diagnosis presented a much more advanced disease stage. Thus, oestrogens are initially protective against CRC, but once developed oestrogens may drive CRC proliferations.

Therefore, the pre-receptor metabolism of oestrogens, namely through steroid sulphatase (STS) and the 17β-hydroxysteroid dehydrogenases (17βHSDs), and the oestrogen receptor status of colonic tissue, most likely influence the incidence and subsequent proliferation of CRC.

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

Disclosure
Society for Endocrinology Early Career Grant.

DOI: 10.1530/endoabs.37.S9.2

S9.3

Abstract unavailable.

DOI: 10.1530/endoabs.37.S9.3

Thyroid and autoimmunity

S10.1

AIRE in thyroid autoimmunity

Terry Smith
University of Michigan Kellogg Eye Center, Ann Arbor, Michigan, USA.

The autoimmune regulator protein (AIRE) is a critical component of thymic education which leads to immune tolerance. Its recent detection in extrathymic tissues has prompted inquiry into potential roles for this protein beyond the thymus. We have reported detecting AIRE in circulating CD34+ fibrocytes, monocyte progenitor cells that are involved in tissue reactivity and remodeling. These fibrocytes have been detected in orbital connective tissue from individuals

with thyroid associated ophthalmopathy and in thyroid tissue from patients with Graves' disease. Further, fibrocytes express functional TSH receptor, thyroglobulin, sodium iodide symporter, and thyroperoxidase. We therefore interrogated these cells for the expression of AIRE and found that both full length and truncated forms of the protein could be detected. When AIRE expression was knocked down with specific targeting SIRNAs, levels of all four thyroid associated proteins were substantially reduced. Analysis of fibrocytes from an individual with APS1 disclosed reduced levels of these proteins as well. These findings suggest that AIRE may play an important role in the expression of thyroid self-antigens outside the thyroid. It is possible that AIRE dependent expression of thyroid antigens by fibrocytes may be involved in the manifestations of Graves' disease such as thyroid associated ophthalmopathy.

DOI: 10.1530/endoabs.37.S10.1

S10.2

Dissecting the function of autoimmune regulator (AIRE)

Pärt Peterson
University of Tartu, Tartu, Estonia.

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

Disclosure

This work was supported by the Estonian Research Council.

DOI: 10.1530/endoabs.37.S10.2

S10.3

Thyroid, selenium and autoimmunity

Lutz Schomburg
Institute for Exper. Endocrinology, Charite Berlin, Berlin, Germany.

The trace element selenium (Se) is unevenly distributed in our earth's crust causing regional differences in soil Se concentrations. Soil Se directly affects plant Se content and thereby animal and human Se intake. Besides intake, the actual health status and genotype modify Se metabolism and expression of selenoproteins, i.e., Se status. In order to assess the individual Se status, total blood Se concentration or two circulating selenoproteins are determined. According to these biomarkers, the majority of Europeans is Se-deficient while e.g. US Americans are sufficiently supplied. This does however not directly translate into an overt clinical phenotype. Nevertheless, several studies have indicated that a Se deficit predisposes to certain diseases. Importantly, some supplementation studies have yielded positive health effects in autoimmune thyroid diseases, but others have not. Only about half of the studies reported remarkable reductions in TPO autoantibodies or improved quality-of-life in Hashimoto's thyroiditis, and one supplementation trial of patients with mild Graves' orbitopathy reported positive effects on quality-of-life and eye disease symptoms – a promising finding which still needs to be replicated. But collectively, the data at hand do not yet advocate general Se supplementation as a therapeutic measure in thyroid autoimmunity. The situation is different when considering epidemiological studies implying that subjects with relatively low Se status have an increased risk for developing goiter, nodules, autoimmune thyroid diseases, infections, cancer and life-threatening complications once severely diseased. These findings – limited as they are – indicate that it appears prudent to avoid a Se deficiency by gentle measures, as successfully done on a population-wide scale in Finland since three decades. It is suggested that preventive biomarker-guided Se supplementation attempts should be considered as a promising health-supporting measure. The talk will raise the awareness for this topic and stimulate a discussion on the respective pros and cons.

Supported by Charité Berlin and Deutsche Forschungsgemeinschaft DFG (Scho849/4-1).

DOI: 10.1530/endoabs.37.S10.3

Hot topics and IESP symposia

S11.1

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

Giampaolo Trivellin[1], Adrian F. Daly[2], Fabio R. Faucz[1], Bo Yuan[3], Liliya Rostomyan[2], Darwin O. Larco[4], Ivana Bjelobaba[5], Letícia F. Leal[1], Marie Helene Schernthaner-Reiter[1], Aggeliki Dimopoulos[1], Prashant Chittiboina[6], Catherine S. Choong[7], Peter Kamenický[8], T. John Wu[4], Stefano Costanzi[9], Benjamin Feldman[10], Stanko S. Stojilkovic[5], James R. Lupski[3], Albert Beckers[2] & Constantine A. Stratakis[1]
[1]Section on Endocrinology and Genetics, Program on Developmental Endocrinology and Genetics (PDEGEN) and Pediatric Endocrinology Inter-institute Training Program, Eunice Kennedy Shriver National Institute, Bethesda, Maryland, USA; [2]Department of Endocrinology and Clinical Genetics, Centre Hospitalier Universitaire de Liège, University of Liège, Liège, Belgium; [3]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas, USA; [4]Department of Obstetrics and Gynecology, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA; [5]Section on Cellular Signaling, Program in Developmental Neuroscience, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health (NIH), Bethesda, Maryland, USA; [6]Surgical Neurology Branch, National Institute of Neurological Diseases and Stroke (NINDS), National Institutes of Health (NIH), Bethesda, Maryland, USA; [7]Department of Paediatric Endocrinology, Princess Margaret Hospital for Children and School of Pediatrics and Child Health, University of Western Australia, Perth, Western Australia, Australia; [8]Université Paris Sud 11, Faculté de Médecine, UMR-S693, Le Kremlin-Bicêtre, France; [9]Department of Chemistry and Center for Behavioral Neuroscience, American University, Washington, District of Columbia, USA; [10]Program in Genomics of Differentiation (PGD), Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health (NIH), Bethesda, Maryland, USA.

Introduction

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

Aim

We studied gigantism for genetic defects.

Methods

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

Results

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

Conclusions

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

Disclosure
This work was funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development.
DOI: 10.1530/endoabs.37.S11.1

S11.2

Abstract unavailable.

DOI: 10.1530/endoabs.37.S11.2

S11.3

Unimolecular combination therapeutics for the treatment of obesity and type 2 diabetes

Matthias Tschöp
Helmholtz Zentrum München, Garching, Germany.

Emerging insights from recent advances in metabolic diseases research suggest that one or several patterns of multiple neuro-endocrine factors are necessary for sustained modulation of body fat or metabolism set points. Gut hormones appear to reside at the core of these master–key-like signaling patterns, as indicated for example by bariatric surgery research. Over the last 7 years, we have therefore tested a large series of combination therapies based on multiple gastrointestinal and adipocyte derived signals. Balanced single molecule peptide hormone based GLP1-glucagon and GIP-GLP1 co-agonists exhibited superior body weight loss and glucose metabolism benefits in mouse models of obesity and diabetes, as compared to any established mono-agonists. Preliminary translational data indicate efficacy of GIP-GLP1 co-agonists in non-human primates. Since co-infusion of a soluble and stable glucagon mono-agonist in parallel with GIP-GLP1 co-agonist treatment provided additional benefits, a series of single molecule GIP-GLP1-glucagon tri-agonists were generated and validated. These novel tri-agonists again showed unprecedented metabolic and body weight benefits in mouse and rat models of obesity and diabetes. In a parallel approach single molecule conjugates combining a peptide (e.g. GLP1) with a steroid (e.g. estrogen) were generated to maximize metabolic benefits and minimize potential toxicity by specifically targeting a subset of estrogen receptors in GLP1-receptor carrying cells. Such peptide carrier based targeting of a specific subset of nuclear hormone receptors was successful: Administration reversed hallmarks of the metabolic syndrome in diet induced obese and insulin resistant mice without causing any detectably side effects or toxicity. The above described novel single molecule approaches to polypharmaceutical therapeutics carry the potential to open new perspectives for the treatment of metabolic diseases such as diabetes and obesity.

DOI: 10.1530/endoabs.37.S11.3

Advances in phaeochromocytoma diagnosis and management (*Endorsed by the European Journal of Endocrinology*)

S12.1

Update on genetics of phaeochromocytoma/paraganglioma

Mercedes Robledo[1,2]
[1]Spanish National Cancer Research Center, Madrid, Spain; [2]ISCIII Center for Biomedical Research on Rare Diseases (CIBERER), Madrid, Spain.

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

DOI: 10.1530/endoabs.37.S12.1

S12.2

Current imaging of pheochromocytoma/paraganglioma

Henri Timmers
Radboud University Medical Centre, Nijmegen, The Netherlands.

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

DOI: 10.1530/endoabs.37.S12.2

S12.3

Outcome of adrenal sparing surgery in heritable pheochromocytoma: the example of multiple endocrine neoplasia type 2

Frederic Castinetti
Department of Endocrinology, La Timone Hospital, Marseille, France.

With the early management of medullary thyroid carcinoma, multiple endocrine neoplasia type 2 has become an example of chronic disease with prolonged follow-up to look for pheochromocytoma diagnosis and appropriate management. In any genetic disease where pheochromocytoma can happen bilaterally, the surgery has long been based on bilateral adrenalectomy (even in the presence of a single pheochromocytoma), and as a consequence on a life long treatment for adrenal insufficiency. Progress has then been made by choosing unilateral adrenalectomy in case of unilateral pheochromocytoma, which now makes sense. Adrenal sparing surgery is probably another step in trying to improve the patients'

overall quality of life. It is a valuable option well described in patients with pheochromocytoma and Von Hippel Lindau's disease. Determining the interest of such a therapeutic approach implies to take into account the risk of recurrence, in comparison with the gain in terms of adrenal function. Moreover, assuming this risk of recurrence implies to characterize the potential of malignancy of hereditary pheochromocytoma, considering that already medullar hyperplastic tissue will remain after surgery. Data on MEN2 patients are scarce in the literature, usually based on a low number of patients, or a short-term follow-up, and this might explain why this approach is still not considered as the gold standard (when technically do-able).
Based on a large international consortium collecting data on 1210 patients with multiple endocrine neoplasia type 2, including more than 500 with pheochromocytoma, we determined the outcome of patients with adrenal sparing surgery in comparison with classical adrenalectomy. Our results emphasized the low rate of adrenal insufficiency, and a relatively low risk of recurrence after a median follow-up of 10 years after adrenal sparing surgery. Interestingly, the rate of recurrence was comparable in patients with classical adrenalectomy, whereas, as expected, the rate of adrenal insufficiency was highly superior with the classical approach. Adrenal sparing surgery is thus clearly a valuable therapeutic option, provided a prolonged and regular follow-up can be maintained (Castinetti et al., Lancet Oncology, 2014).

DOI: 10.1530/endoabs.37.S12.3

New concepts in Vitamin D research

S13.1

Abstract unavailable.

DOI: 10.1530/endoabs.37.S13.1

S13.2

Clinical consequences of low vitamin D status

Kevin Cashman
Vitamin D Research Group, School of Food and Nutritional Sciences and Department of Medicine, University College Cork, Cork, Ireland.

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

DOI: 10.1530/endoabs.37.S13.2

S13.3

Abstract unavailable.

DOI: 10.1530/endoabs.37.S13.3

S13.4

Abstract unavailable.

DOI: 10.1530/endoabs.37.S13.4

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

S14.1

Adipose tissue turnover in humans

Kirsty Spalding
Karolinska Institute, Stockholm, Sweden.

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

DOI: 10.1530/endoabs.37.S14.1

S14.2

FGF1 and PPAR-γ in the Adipocyte

Johan Jonker
University Medical Center Groningen, Groningen, The Netherlands.

Survival requires the ability to adapt to cycles of feast and famine, yet the underlying mechanisms to maintain metabolic balance during extremes of nutrient excess remain poorly understood. We recently discovered that the classic growth factor FGF1 is induced in white adipose tissue (WAT) in response to high-fat-diet (HFD) and repressed during fastong, pointing to an unexpected metabolic function. Thus, FGF1 participates in both fed-state and fasted-state responses. In WAT, FGF1 is induced by HFD through a PPAR-γ dependent mechanism and thus is also responsive to PPARg drugs such as Actos and Avandia. Mice with a deficiency in FGF1, when challenged with a HFD, develop an aggressive diabetic phenotype, resulting from adipose that is unable to expand, which progressively becomes inflamed, fibrotic and necrotic and is simply unable to adapt to nutrient stress.
As loss of FGF1 by knockout results in a diabetic phenotype, we speculated that increasing FGF1 levels by direct injection in diabetic mice, could potentially have anti-diabetic effects. As a proteoglycan binding protein, endogenous FGF1 is normally locally restricted. Upon 'endocrinization' of FGF1 by simple injection into the body of obese diabetic mice we found potent glucose lowering and insulin sensitizing effects. Thus, more that 30 years after its discovery as a growth factor, 'endocrinization' of FGF1 in a diabetic mouse, uncovers a potent yet hidden insulin sensitizing activity with great potential as a new therapy in the treatment of metabolic disease.

DOI: 10.1530/endoabs.37.S14.2

S14.3

Manipulating adipose tissue sensitivity to glucocorticoid excess

Gareth Lavery
University of Birmingham, Birmingham, UK.

Glucocorticoids (GCs) have physiological actions in almost all tissues, classically mediated by the GC receptor. The potent effects of GCs upon metabolic phenotype are best exemplified in patients with circulating GC excess (Cushing's syndrome), who develop central (visceral) obesity, insulin resistance, myopathy, hypertension and in some cases overt type 2 diabetes (T2DM) and non alcoholic fatty liver disease (NAFLD). GCs are one of the most frequently prescribed class of medication, with 2–3% of UK and US populations currently receiving GC therapy. The clinical efficacy of GC therapy is not in doubt, but their 'cushingoid' side effects create significant morbidity and mortality and current prevention strategies to reduce the adverse metabolic consequences are limited. Tissue-specific availability of GC to bind and activate the GR is controlled by a series of pre-receptor regulatory enzymes. 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) regenerates the active GC cortisol from inactive cortisone (corticosterone and 11-dehydrocorticosterone respectively in rodents) in adipose tissue, liver and muscle. Indeed, changes in GC availability, notably in adipose tissue, contribute significantly to the development of an adverse metabolic phenotype. Genetic and pharmacological inhibition of 11β-HSD1 in rodent and clinical studies improves the metabolic profile in obesity and T2DM models. This presentation will address how 11β-HSD1 contributes to promoting the unwanted metabolic aspects of GC excess and the 'cushingoid' phenotype often seen in patients taking GC therapy, with particular emphasis on adipose tissue specific GC effects. We propose that 11β-HSD1 inhibition may offer protection from a deleterious metabolic profile in the context of the GC excess state.

DOI: 10.1530/endoabs.37.S14.3

Puberty: new mechanisms

S15.1

Epigenetics of Female Puberty

Sergio Ojeda, Alejandro Lomniczi, Hollis Wright & Carlos Toro
Oregon National Primate Research Center/Oregon Health & Science University, Beaverton, OR, USA.

A prevailing concept regarding the mechanism controlling the timing of puberty proposes that GnRH release from the hypothalamus increases at puberty due to a loss of transsynaptic inhibition, accompanied by an increase in neuronal/glial excitatory inputs to GnRH neurons. Without negating the importance of this intercellular communication process, recent evidence suggests that a critical inhibitory/excitatory Yin-Yang mechanism regulating the advent of puberty is epigenetic in nature and affects the transcriptional activity of neurons involved in stimulating GnRH release (such as kisspeptin neurons). The repressive arm of this mechanism is provided by the Polycomb group (PcG) of transcriptional silencers, which prevents the premature initiation of female puberty by silencing the *Kiss1* gene in kisspeptin neurons of the arcuate nucleus (ARC) of the hypothalamus. At the end of juvenile development PcG proteins are evicted from the *Kiss1* promoter and the abundance of the PcG-catalyzed, 'repressive', histone modification H3K27me3 is reduced. The antagonistic counterpart of PcG-mediated gene silencing is provided by the Trithorax (TrxG) group of transcriptional activators. Like the PcG complex, TrxG genes are expressed in kisspeptin neurons of the ARC. Key TrxG proteins required for the synthesis of 'activating' histone marks (histone 3 di- and trimethylated at lysine 4) are recruited to the *Kiss1* promoter at the initiation of puberty and this correlates well with an increased abundance of the activating histone marks H3K4me3 and histone 3 acetylated at lysine 9 and 4 (H3K9, 14 ac) at the promoter. Both the PcG and the TrxG systems are, in turn) regulated by upstream repressors. Whereas PcG gene expression is inhibited by members of the POK (for POZ and Krüppel) family of transcriptional regulators, TrxG action is attenuated by zinc finger (ZNF) proteins that facilitate the demethylation of H3K4me2 *via* recruitment of a specific lysine demethylase (Kdm1a/LSD1) to the *KISS1* and *TAC3* promoters. The presence of this tight system of epigenetic regulation in *KISS1/TAC3* expressing neurons of the ARC suggests that a switch from epigenetic repression to activation within these neurons underlies the developmental process by which GnRH release is first kept in check before puberty, and then increases by late juvenile development to bring about the pubertal process. (NSF grant 1121691)

Disclosure
National Science Foundation (USA) Grant IOS1121691.

DOI: 10.1530/endoabs.37.S15.1

S15.2

GnRH development and function: lessons from semaphorins

Paolo Giacobini[1,2]
[1]Inserm, Laboratory of Development and Plasticity of the Neuroendocrine Brain, Jean-Pierre Aubert Research Centre, U1172, Lille, France;
[2]University of Lille, School of Medicine and Institut de Medecine Predictive et de Recherche Therapeutique (IMPRT-IFR114), Lille, France.

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

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

In recent years several studies have started to shed light on the role of semaphorins in the motility, survival and axonal plasticity of GnRH neurons.

This talk will review some of these studies, which provided insight into the sophisticated molecular mechanisms that allow for the spatiotemporal control of the responsiveness to semaphorins of developing GnRH neurons. Genetic data are also presented to show that some forms of reproductive disorders in humans are associated with mutations in specific classes of semaphorin family members.

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

Disclosure
This work was supported by the Institut National de la Sante et de la Recherche Medicale, Inserm, France (grant number U837), Agence Nationale de la Recherche, ANR, France (grant numbers ANR-2010-JCJC-1404 – 01 and ANR-14-CE12-0015-01 RoSes).

DOI: 10.1530/endoabs.37.S15.2

S15.3

Genetic regulators of the timing of puberty

Ken Ong
University of Cambridge, Cambridge, UK.

The timing of puberty varies widely between individuals and in girls early puberty timing is associated with higher risks for adult obesity, type 2 diabetes (T2D), cardiovascular disease (CVD), breast cancer and all-cause mortality. Understanding the regulation of puberty timing therefore has relevance to disease pathogenesis as well as developmental and human biology. Large-scale genome-wide association studies have identified robust evidence for more than 100 independent genomic association signals associated with age at menarche, including overlap with genes that are disrupted in rare disorders of puberty. Such findings have implicated RNA-mediated gene silencing, histone regulation of gene activity, and retinoic acid-related nuclear receptors among novel mechanisms that regulate puberty timing. Menarche signals are enriched in imprinted gene regions and three imprinted loci (*DLK1/WDR25*, *MKRN3/MAGEL2*, and *KCNK9*) demonstrated parent-of-origin specific associations concordant with their known parental expression patterns; these findings indicate parental conflicts over the selective advantages of puberty timing. Recent findings provide evidence for a substantially shared genetic aetiology of puberty timing between males and females, and also indicate causal relationships between earlier puberty timing and higher BMI, T2D, and CVD, which are likely mediated by both BMI-related and BMI-independent mechanisms.

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

DOI: 10.1530/endoabs.S15.3

Pathogenesis of adrenocortical tumours

S16.1

Inherited tumour syndromes and adrenal cancer

Tobias Else
University of Michigan, Ann Arbor, MI, USA.

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

DOI: 10.1530/endoabs.37.S16.1

S16.2

Role of steroidogenic factor-1 in the pathogenesis of adrenocortical tumours

Mabrouka Doghman[1,2] & Enzo Lalli[1,2]
[1]IPMC CNRS, Sophia Antipolis, France; [2]LIA NEOGENEX CNRS, Sophia Antipolis, France.

Steroidogenic factor-1 (SF-1, NR5A1) is a transcription factor that plays an essential role in the development of adrenal glands and gonads. Multiple level regulation of SF-1 activity is exerted by interaction with cofactors, post-translational modifications and epigenetic gene expression regulation. Our studies involving both cell lines and transgenic mouse studies showed that an increased SF-1 dosage activates adrenocortical cell proliferation and causes adrenocortical neoplasia. By employing multiple genomic approaches, we defined different levels of regulation in transcriptome, miRNome and more recently on regulome exerted by SF-1 dosage. We identified new functional interactions between SF-1 and neuron-restrictive silencer factor/RE1-silencing transcription factor (NRSF/REST) suggesting that SF-1 has a broader role than initially thought in regulating tissue-specific gene expression programs.
We showed that SF-1 dosage differentially regulates the expression of numerous and distinct genes, involved in a variety of biological processes, suggesting that fine regulation of SF-1 dosage is a critical determinant of its action during adrenal development, function and tumourigenesis.
We identified fetal and adult testis expressed-1 (FATE1), a cancer testis antigen (CTA), as a new dosage-dependent target of SF-1. CTAs are emerging as attractive targets for therapeutic cancer vaccines due to their expression in tumors but not in normal tissues except testis. Our recent studies aim to better understand the role of FATE1 in tumor cellular metabolism, mitochondrial morphology and signaling and in drug resistance, potentially important for the aggressive phenotype of adrenocortical carcinoma.
Our project aims to investigate the involvement of these new SF-1 target genes in adrenal pathophysiology to improve the diagnostic of ACC and in the future to develop innovative strategies for cancer treatment.

Disclosure
This work has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement no 259735 (ENS@T-CANCER).

DOI: 10.1530/endoabs.37.S16.2

S16.3

miRNA as biomarkers in adrenal cancer?

Peter Igaz
Semmelweis University, Budapest, Hungary.

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

Disclosure
Hungarian Scientific Research Grant (OTKA K100295).

DOI: 10.1530/endoabs.37.S16.3

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

S17.1

Diabetes and osteoporosis – cause for concern?

Peter Vestergaard
Aalborg University Hospital, Aalborg, Denmark.

Background
Diabetes and osteoporosis are both frequent conditions, a link may thus put a substantial number of patients at risk of fragility fractures and the consequences of these such as pain, disability, and increased mortality. Skeletal fragility and osteoporosis may represent a hitherto overlooked complication of diabetes in line with say diabetic eye disease, diabetic nephropathy etc.
Findings
An increased risk of fractures has been observed in both type 1 and type 2 diabetes. In type 1 diabetes, a decreased bone density has been observed, while in type 2 diabetes, bone density may actually be increased. A discrepancy seemingly exists between bone density and fracture risk in diabetes, especially in type 2 diabetes. The increase in fracture risk has been observed at the hip, spine, and forearm as well as for overall risk of fractures. Especially the risk of hip fractures seems increased in type 1 diabetes, whereas the increase is less pronounced in type 2 diabetes. Hypoglycemia seems to play a minor role for the occurrence of fractures. The increase in fracture risk seemingly is related to diabetes *per se* and less so to complications (say falls related to diabetic eye disease).
Conclusions
An increased risk of fractures – in particular hip fractures, which may be associated with significant excess mortality and morbidity – may be present. The increase may be linked to skeletal frailty resulting from metabolic disruptions stemming from impaired glucose metabolism rather than from falls related to hypoglycemia or say reduced eye sight.

DOI: 10.1530/endoabs.37.S17.1

S17.2

Pathophysiology of diabetoporosis

Serge Ferrari
Geneva University Hospital, Geneva, Switzerland.

Both type 1 and 2 diabetes are associated with an increased fracture risk. Whereas in type 1 bone fragility is mostly explained by a lower peak bone mass and low bone turnover state, which is a common feature of several chronic and/or inflammatory diseases starting during growth, in type 2 diabetes there is not necessarily low bone mass, rather a higher aBMD related to overweight/obesity in

these subjects. To explain the increased propensity to fractures in this case, a higher risk of falls and decreased bone quality have both been advocated. The latter includes alterations in collagen crosslinks by advanced glycation end-products (AGEs) such as pentosidine; higher sclerostin levels associated with low bone formation; and microstructural alterations, particularly an increased cortical porosity. The molecular mechanisms relating glucose, fat and bone metabolism appear increasingly complex. They involve the transcription factor Ppar gamma, which promotes fat accumulation at the expenses of bone forming cells; Wnt-beta-catenin signaling; inflammatory factors, -i.e. interleukins-, and adipokines, -such as leptin and adiponectin-, that influence both insulin resistance and bone loss; and bone-derived molecules, including (undecarboxylated) osteocalcin and RANK Ligand, both recently found to regulate glucose metabolism. Moreover, genome wide association studies (GWAS) have started to unveil common genes that exert pleiotropic effects on the susceptibility to both diabetes and osteoporosis.

DOI: 10.1530/endoabs.37.S17.2

S17.3

Clinical management of fragile bone in type 2 diabetes

Eugene McCloskey
[1]University of Sheffield, Sheffield, UK; [2]CIMA, University of Sheffield, Sheffield, UK.

Given the increasingly accepted increase in fracture risk that occurs in patients with type 2 diabetes, a number of strategies need to be considered reflecting the multiple factors underlying the fracture risk. These comprise measures to improve falls risk, the avoidance of treatments that may be detrimental to skeletal health and the use of treatments to maintain or improve bone strength.

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

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

DOI: 10.1530/endoabs.37.S17.3

New genetics of pituitary tumours (*Endorsed by the European Journal of Endocrinology*)

S18.1

A novel role for stem cells in the regulation of turnover in the postnatal pituitary

Cynthia Andoniadou
King's College London, London, UK.

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

DOI: 10.1530/endoabs.37.S18.1

S18.2

Abstract unavailable.

DOI: 10.1530/endoabs.37.S18.2

S18.3

Genetics of Cushings Disease

Martin Reincke
Medizinische Klinik und Poliklinik IV, Klinikum der LMU, München, Germany.

Cushing's disease is caused by corticotroph adenomas of the pituitary. To explore molecular mechanisms of endocrine autonomy, we recently performed exome sequencing of 10 corticotroph adenomas[1] identifying somatic mutations in the USP8 deubiquitinase gene in 4 of 10 adenomas. The mutations clustered in the 14-3-3 protein binding motif enhancing proteolytic cleavage and catalytic activity of USP8. Cleaved USP8 led to increased EGF receptor deubiquitination impairing its downregulation and sustaining EGF signaling. USP8 mutants enhanced promoter activity of the gene for proopiomelanocortin. Our data show that dominant mutations in USP8 cause Cushing's disease *via* activation of EGF receptor signaling. In a follow-up study we performed a retrospective, multicentric, genetic analysis of 134 functioning and 11 silent corticotroph pituitary adenomas using Sanger sequencing. Clinical data from these patients have been collected and examined within the context of the mutational status of USP8. Somatic mutations in USP8 were found in 48 (36%) adenomas from patients with Cushing's disease, but in none of the 11 silent corticotropinomas. The prevalence was higher in adults than in pediatric cases and in females than in males. Adults having USP8-mutated adenomas were diagnosed at an earlier age (36 vs 44 years) than those with wild-type adenomas. Future research will be directed towards therapeutic targeting of USP8 in corticotroph adenomas.

Reference
1. Reincke M, *et al*. Mutations in the deubiquitinase gene USP8 cause Cushing's disease. *Nat Genet.* 2015 Jan; **47**(1):31–8. doi:10.1038/ng.3166. Epub 2014 Dec 8.

DOI: 10.1530/endoabs.37.S18.3

Metabolic dysfunction in PCOS

S19.1

Genetic determinants of metabolic dysfunction in PCOS

Jerome Strauss[1] & Jan McAllister[2]
[1]Virginia Commonwealth University, Richmond, Virginia, USA; [2]Pennsylvania State Hershey College of Medicine, Hershey, Pennsylvania, USA.

PCOS is a common disorder that is reported to affect 5–7% of women of reproductive age. Although there has been debate about the diagnostic criteria for

PCOS, hyperandrogenemia/hyperandrogenism, not explained by other causes, is a hallmark of the disorder, and it is included as an essential element in all 'consensus' diagnostic schemes. Studies on cultures of human theca cells derived from normal and PCOS women have demonstrated that PCOS theca secretes greater amounts of androgen than theca tissue or cells from regularly ovulating women. Increased *CYP17A1* (P450 17α-hydroxylase/17,20-lyase) gene expression in PCOS theca cells is associated with excess androgen production. Our previous molecular characterization of PCOS theca cells and normal theca cells from multiple individuals by microarray analysis and quantitative PCR established that normal and PCOS theca cells have distinctive molecular signatures, suggesting intrinsic (genetic) differences. A major milestone was achieved with the publication of a genome-wide association studies (GWAS) on Han Chinese, which identified eleven loci, including *DENND1A, a* finding that was subsequently validated in European populations. DENND1A is a clathrin binding protein found in coated pits, and which positions it to modulate cell surface receptor signal transduction. Using cultured human theca cells, we have shown that an isoform of DENND1A, V2, is over-expressed in PCOS theca cells compared to theca cells derived from ovaries of normally cycling women. V2 overexpression in PCOS may be the result of alternative splicing. Forced expression of V2 increases androgen production, and *CYP17A1* mRNA in normal theca cells, whereas knock-down of V2 expression reduces androgen secretion and *CYP17A1* mRNA in PCOS theca cells. Both humanized monoclonal antibodies against V2, and their Fab fragments, also reduce androgen production and *CYP17A1* mRNA when added to cultured PCOS theca cells. DENND1A V2 can be placed into a network of genes identified in the Chinese GWAS that can explain the hyperandrogenemia phenotype of PCOS.

Disclosure
NIH grants U54HD034449, R01HD058300, and R01HD033852.

DOI: 10.1530/endoabs.37.S19.1

S19.2

The role of androgens in PCOS-related insulin resistance

Michael O'Reilly[1], Jeremy Tomlinson[2], Robert Semple[3] & Wiebke Arlt[1]
[1]University of Birmingham, Birmingham, UK; [2]University of Oxford, Oxford, UK; [3]University of Cambridge, Cambridge, UK.

Insulin resistance and androgen excess are the cardinal features of polycystic ovary syndrome (PCOS). The severity of hyperandrogenism and metabolic dysfunction in PCOS are closely correlated but the underlying mechanisms are poorly understood. Aldoketoreductase type 1C3 (*AKR1C3*) is an important source of adipose androgen generation (converting androstenedione to testosterone) and we have postulated that it may have a critical role linking androgen metabolism and metabolic phenotype in PCOS.

Ten patients with PCOS, three with insulin receptor (INSR) mutations and ten control patients underwent oral DHEA challenge with concomitant adipose tissue microdialysis. Serum and adipose androgens, and adipose glycerol levels, were sampled every 30 minutes for 4 h. In parallel, adipose androgen generation (measured using LC/MS-MS), was studied using primary cultures of human adipocytes and the preadipocyte SGBS cell line. The impact of androgens upon metabolic adipocyte phenotype was assessed through measurement of adipose lipogenesis, free fatty acid uptake (FFA) and β-oxidation.

After oral DHEA, area under curve (AUC) for serum testosterone (T) was higher in PCOS patients than controls, but highest in patients with INSR mutations, suggesting enhanced *AKR1C3* activity. Adipose dihydrotestosterone (DHT) was detectable in adipose interstitial fluid and was higher in PCOS patients than controls. Furthermore, adipose tissue interstitial glycerol levels were decreased in PCOS patients. Subcutaneous adipose *AKR1C3* mRNA expression correlated strongly with BMI. In human adipocytes, insulin up-regulated *AKR1C3* expression and activity. T increased *de novo* lipogenesis, while both T and DHT increased FFA uptake and suppressed β-oxidation.

Hyperinsulinaemia may drive adipose androgen generation through increased expression and activity of AKR1C3, with consequences for adipocyte function, driving lipogenesis and increasing free fatty acid uptake. Resultant adipocyte hypertrophy could lead to increased insulin resistance, fuelling a vicious circle of hyperinsulinaemia, adipose androgen generation and increased lipid accumulation.

Disclosure
This work was supported by the Wellcome Trust (Clinical Research Training Fellowship 099909 to Dr. Michael O'Reilly).

DOI: 10.1530/endoabs.37.S19.2

S19.3

Abstract unavailable.

DOI: 10.1530/endoabs.37.S19.3

Endocrine consequences of childhood cancer treatment

S20.1

Reproductive function in cancer survivors

W Hamish Wallace
University of Edinburgh, Edinburgh, UK.

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

DOI: 10.1530/endoabs.37.S20.1

S20.2

Hypopituitarism in cancer survivors

Eva Marie Erfurth
Clinal Sciences, Medical Faculty of Lund University, Lund, Sweden.

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

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

Disclosure
Swedish Childhood Cancer Foundation.

DOI: 10.1530/endoabs.37.S20.2

S20.3

Late effects of cancer treatment on cardiovascular risk

Francesco Felicetti[1,2]
[1]Transition Unit for Childhood Cancer Survivors, AOU Città della Salute e della Scienza, Turin, Italy; [2]Department of Medical Science, University of Torino, Turin, Italy.

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

DOI: 10.1530/endoabs.37.S20.3

S20.4

Abstract unavailable.

DOI: 10.1530/endoabs.37.S20.4

S20.5

Secondary cancers in childhood cancer survivors

Raoul Reulen
University of Birmingham, Birmingham, UK.

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

DOI: 10.1530/endoabs.37.S20.5

Thyroid hormone in pregnancy

S21.1

Abstract unavailable.

DOI: 10.1530/endoabs.37.S21.1

S21.2

Consequences of maternal thyroid dysfunction for offspring

John Lazarus
Cardiff University, Cardiff, UK.

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

DOI: 10.1530/endoabs.37.S21.2

S21.3

Thyroid hormone in brain development

Juan Bernal
Instituto de Investigaciones Biomedicas, CSIC, and Center for Biomedical Research on rare Diseases, Madrid, Spain.

Thyroid hormones (T_4 and T_3) have a major role in brain development, and their deficits during critical stages during the fetal and neonatal periods may cause profound intellectual and neuromotor deficits. A particular example is the X-linked Allan-Herndon-Dudley syndrome, caused by mutations of the cellular transporter for thyroid hormone MCT8 (SLC16A2). In this presentation I will first review the pathophysiology of thyroid hormone transport and metabolism in the brain, and the interaction between the main players, i.e., the transporters, the deiodinases, and the nuclear receptors. Then I will review how thyroid hormone (T_3) acts at the genomic level by regulating the expression of many genes. In particular I will present recent data from our laboratory using primary mouse cerebrocortical cells in culture that has permitted the identification of primary and secondary gene responses after T_3 addition. Genomic data indicate that the role of thyroid hormone is to facilitate the transition from a fetal pattern to a mature or adult pattern of gene expression.
Disclosure
This work was supported by the Plan Nacional grant SAF2011-25608, the Center for Biomedical Research on rare Diseases, and the ERA-Net E-Rare2, the European Research Projects on rare Diseases.

DOI: 10.1530/endoabs.37.S21.3

Beta cell biology

S22.1

Noncoding genome function in pancreas development and disease

Jorge Ferrer
Imperial College, London, UK.

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

DOI: 10.1530/endoabs.37.S22.1

S22.2

Novel therapeutic targets in the β-cell

Thomas Mandrup-Poulsen[1,2]
[1]University of Copenhagen, Copenhagen, Denmark, [2]Karolinska Institute, Stockholm, Sweden.

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

References

1. Hansen JB, Tonnesen MF, Madsen AN, Hagedorn PH, Friberg J, Grunnet LG, Heller RS, Nielsen AØ, Størling J, Bayens L, Anker-Kitai L, Quortrup K, Bouwens L, Efrat S, Aalund M, Andrews N, Billestrup N, Karlsen E, Holst B, Pociot F, Mandrup-Poulsen T. Divalent metal transporter 1 regulates iron-mediated ROS and pancreatic β-cell fate in response to cytokines. Cell Metab 2012; **16**: 1-13.
2. Ellervik C, Mandrup-Poulsen T, Andersen HU, Tybjærg-Hansen A, Frandsen M, Birgens H, Nordestgaard BG. Elevated transferrin saturation and risk of diabetes mellitus – three population-based studies. *Diabetes Care* 2011;**34**: 2256-2258.

DOI: 10.1530/endoabs.37.S22.2

S22.3

Novel models of human pancreatic beta cells

Philippe Ravassard
ICM, CNRS UMR 7225, Paris, France.

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

Disclosure
Research was supported by CNRS, INSERM and Endocells and by grants from the Seventh Framework Program of the European Union (no. 241883), from the Innovative Medicines Initiative Joint Undertaking under grant agreement (no. 155005; IMIDIA).

DOI: 10.1530/endoabs.37.S22.3

Adrenal insufficiency: advances in diagnostics and therapy (*Endorsed by the European Journal of Endocrinology*)

S23.1

How to diagnose adrenal insufficiency in critical illness?

Eva Boonen
KU Leuven, Leuven, Belgium.

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

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

DOI: 10.1530/endoabs.37.S23.1

S23.2

Regenerative therapy in autoimmune Addison's disease

Simon Pearce
Newcastle University, Newcastle upon Tyne, UK.

It is obvious that adrenal cortex is plastic, with adrenal atrophy and functional hypoadrenalism during exogenous glucocorticoid therapy; yet adrenal hyperplasia and hyperfunction during stimulation from ACTH during Cushing's disease. This is owing to subcapsular adrenocortical stem cells that regenerate the zones of adult adrenal cortex throughout life.

We have performed a series of experimental medicine trials in order to explore the idea that autoimmune Addison's disease may therefore be remediable. These

studies have used either immunomodulation with B lymphocyte depletion therapy, high-dose ACTH analogue or both, in order to try to modify the natural history of the condition. In summary, there are a proportion of people (~20%) with both newly diagnosed and established autoimmune Addison's disease who have some degree of residual adrenal function. In a few people we have induced a durable, steroid medication-free remission of Addison's disease which has lasted from 6 months to as long as 4 years and ongoing. This opens a window for further regenerative medicine strategies to ameliorate adrenal failure in this patient group.

DOI: 10.1530/endoabs.37.S23.2

S23.3

Cortisol measured in scalp hair as a monitoring tool for systemic cortisol levels

Elisabeth van Rossum
Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands.

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

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

Disclosure
This work was supported by the Netherlands Organisation for Scientific Research (NWO) (grant number 916.96.069), Thrasher Research Fund (grant number TRF11643), the Netherlands Brain Foundation (grant number F2011(1)-12), and an Erasmus MC Fe.

DOI: 10.1530/endoabs.37.S23.3

Androgens and disease progression in prostate cancer

S24.1

Leveraging circulating DNA studies to identify mechanisms of resistance to CYP17A1 inhibition

Gerhardt Attard
The Institute of Cancer Research and the Royal Marsden, London, UK.

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

DOI: 10.1530/endoabs.37.S24.1

S24.2

Abstract unavailable.

DOI: 10.1530/endoabs.37.S24.2

S24.3

Abstract unavailable.

DOI: 10.1530/endoabs.37.S24.3

Challenges in pituitary tumours

S25.1

Treatment with temozolomide in aggressive pituitary tumours with or without metastases

Gerald Raverot[1,2,3]
[1]Hospices Civils de Lyon, Lyon, France; [2]Université Lyon, Lyon, France; [3]INSERM U1028, Lyon, France.

Aggressive pituitary tumours, characterized by tumor recurrence and continued progression despite repeated treatments and pituitary carcinomas respond poorly to conventional therapies. The first reports describing the successful use of temozolomide (TMZ), an orally administered alkylating agent used to treat malignant gliomas, in the management of pituitary carcinomas were published in 2006. Following these single case reports small series of patients have detailed the successful use of TMZ, in the management of these pituitary tumours with an initial response in about 40–60% of cases some. Rapid tumour shrinkage or hormonal response to temozolomide treatment is usually observed within weeks after treatment initiation in responding patients. As a consequence, the lack of response after three cycles predicts further resistance to this treatment. Despite these encouraging results, complete tumour regression are exceptional, and secondary resistance are common during follow-up.

O6-methylguanine-DNA methyltransferase (MGMT), a DNA repair system involved in the cellular defence, represents the major mechanism of resistance to temozolomide. It has been suggested that MGMT expression may predict the tumour response to TMZ. Although results are conflicting among publication, it is accepted that low MGMT staining is associated with a high likelihood of treatment response. Owing to the rarity of the condition, contradictory published results, absence of prospective study and lack of other available medical treatments, MGMT status should probably not be taken as a reason to deny these patients the potential benefit of temozolomide. The expression of MLH1, MSH2, MSH6, three proteins of the DNA mismatch repair system, have been examined by IHC in three studies but these results are too preliminary and discordant to guide therapeutic options.

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

DOI: 10.1530/endoabs.37.S25.1

S25.2

Abstract unavailable.

DOI: 10.1530/endoabs.37.S25.2

S25.3

Abstract unavailable.

DOI: 10.1530/endoabs.37.S25.3

Towards the bionic pancreas: will the journey end?

S26.1

Abstract unavailable.

DOI: 10.1530/endoabs.37.S26.1

S26.2

Continuous glucose monitoring systems

Tadej Battelino[1,2]
[1]University Children's Hospital, Ljubljana, Slovenia; [2]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia.

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

Several randomised controlled trials (RCT) demonstrated a clinically meaningful reduction in glycated haemoglobin A1c with the use of CGM. A meta-analysis based on individual patients' data demonstrated that the reduction in A1c is most pronounced in patients with poor metabolic control and when CGM is used most of the study time. The reduction of A1c was significant when CGM was used with multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII). In more recent RCTs, a reduction of A1c was associated with a concomitant reduction of time spent in hypoglycaemia.

CGM can be used with CSII combined in a single device. RTCs comparing sensor-augmenting insulin pumps (SAP) to MDI or CSII demonstrated a significant and clinically meaningful decrease in A1c. Moreover, a SAP can include an automated insulin delivery suspension on pre-selected low glucose threshold. This automated insulin delivery suspension feature was demonstrated in RCTs to reduce both hypoglycaemia and severe hypoglycaemia across all age groups of people with diabetes.

Finally, CGM can be used as a part of an artificial pancreas. RCTs using different algorithms for closed-loop insulin delivery based on CGM demonstrate both improvement in metabolic control and reduction in hypoglycaemia.

Currently available CGM systems still have quite a few technical limitations, related to the subcutaneous sensors, wireless connectivity, signal strength, accuracy and reliability. Further improvements are needed along with a continuous safety and quality surveillance for a sustained long term use of CGM that will empower people with diabetes for a more flexible, less burdensome and successful metabolic control.

Disclosure
Slovenian National Research Agency grants J3-2412, J3-9663 and P3-0343.
DOI: 10.1530/endoabs.37.S26.2

S26.3

Artificial Pancreas

J Hans DeVries
Academic Medical Center at the University of Amsterdam, Amsterdam, The Netherlands.

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

Disclosure
This work was supported by the European Commission, under the FP7 program, grant number 247138.
DOI: 10.1530/endoabs.37.S26.3

Thyroid cancer: new development in diagnosis and treatment (*Endorsed by the European Journal of Endocrinology*)

S27.1

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

Antonio Sitges-Serra
Hospital del Mar, Barcelona, Spain.

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

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

Because the rate of central lymph node metastasis increases with tumour size, we advocate to add routine CND to total thyroidectomy in all PTC >1 cm; preferentially bilateral if performed for therapeutic purposes and unilateral when performed prophylactically. In our hands, this optimized surgical approach has resulted in a low 9% recurrence rate after a mean follow-up of seven years in over

150 patients (mean T size 27 mm) with a 7.5 and 2.5% permanent hypopara rates for therapeutic and prophylactic CND respectively. All recurrences have occurred in the lateral neck (despite prior radioiodine treatment) and none in compartment VI. 30% of our patients were not treated with radioiodine; none of them has developed a recurrence.

DOI: 10.1530/endoabs.37.S27.1

S27.2

Abstract unavailable.

DOI: 10.1530/endoabs.37.S27.2

S27.3

Abstract unavailable.

DOI: 10.1530/endoabs.37.S27.3

Hormones and immunity in pregnancy

S28.1

Hormonal modulation of immune responses during pregnancy

Ana Claudia Zenclussen
Experimental Obstetrics and Gynecology, Medical Faculty, Otto-von-Guericke University, Magdeburg, Germany.

Pregnancy is a puzzling phenomenon for researches as it defies the rules of immunology. The immune system of a pregnant woman is able to both tolerate the foreign while being alert to possible harm. It is now known that paternal antigens expressed by the fetus are not ignored but actively tolerated by the maternal immune system. Pregnancy hormones may have a pivotal role on the modulation of immune cell functions. We have described the important participation of the pregnancy hormone human chorionic gonadotropin (hCG) in the regulation of immune responses during pregnancy. During this lecture, special emphasis will be put on the modulation of regulatory T cells and regulatory B cells. Data obtained from animal models as well as from patient's samples will be discussed.

Disclosure
This work was supported by the German Research Council ZE 526/7-1.

DOI: 10.1530/endoabs.37.S28.1

S28.2

Sex hormones and B cells in pregnancy

Federico Jensen
Laboratory for Immunology of Pregnancy Center for Pharmacalogical and Botanical Studies (CEFYBO-CONICET-UBA), Buenos Aires, Argentina.

Mammalian pregnancy is characterized by tremendous changes and adaptations in the endocrine as well as in the immune system. Early in pregnancy, levels of female sex hormones, progesterone (P_4) and estradiol (E_2) produced by the corpora lutea (CL) significantly rise, promoting huge modifications of the uterine epithelium ensuring embryo implantation. Once the embryo is implanted, trophoblast cells produce and release increasing levels of human chorionic gonadotropin (hCG), which among other functions stimulates the CLs to continue producing progesterone. Simultaneously, the maternal immune system undergoes several adaptations; e.g., expansion of regulatory B and T cells, tending to 'accept' the presence of the semi-allogeneic fetus expressing foreign antigens.
These modifications and adaptations of the endocrine and immune system are not independent of each other but highly coordinated. Indeed, alongside with the above-mentioned functions, female sex hormones actively participate in the process of shaping immune cells toward a transient state of tolerance necessary for the maintenance of pregnancy.
B-lymphocytes are pleiotropic cells belonging to the adaptive arm of the immune system. Besides their well-known function as antibody-producing cells, B-lymphocytes can produce a broad variety of cytokines as well as present antigens to T cells, thus they have a central role in regulating an immune response. In this talk I will present and discuss different mechanisms of how female sex hormones influence and coordinate B cell functionality in the context of pregnancy.

Disclosure
This study was supported by grants from the Fritz Thyssen Foundation to FJ (Az. 10.12.2.155) and intramural founding from Medial Faculty, Greifswald University.

DOI: 10.1530/endoabs.37.S28.2

S28.3

Vitamin D and pregnancy outcome

Nicholas Harvey
MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK.

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

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

DOI: 10.1530/endoabs.37.S28.3

Management of endocrine transition

S29.1

Abstract unavailable.

DOI: 10.1530/endoabs.37.S29.1

S29.2

Management of endocrine transition

Philippe Touraine
Department of Endocrinology and Reproductive Medicine, Hôpital Pitie Salpetriere, Paris, France.

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

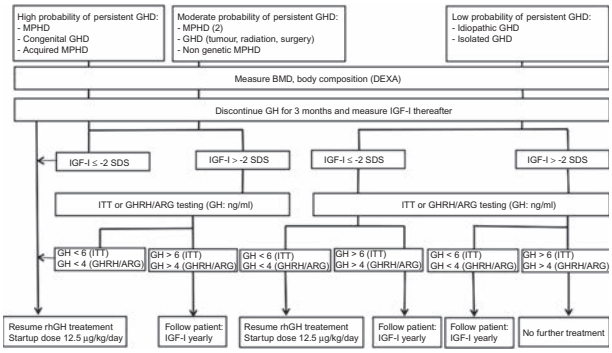
DOI: 10.1530/endoabs.37.S29.2

S29.3

GH deficiency: the transition from childhood/adolescence to adulthood

Primus-E Mullus
Paediatric Endocrinology, Diabetology and Metabolism, University Children's Hospital, Inselspital, CH-3010 Bern, Switzerland.

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



DOI: 10.1530/endoabs.37.S29.3

S29.4

Prader–Willi syndrome

Charlotte Höybye
Karolinska University Hospital, Stockholm, Sweden.

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

Endocrine deficiencies

The combination of the phenotype and reduced GH and IGF1 levels indicates a dysfunction in the GH/IGF1 axis. The degree of GH deficiency varies from mild to severe. GH treatment initiated during childhood normalises skeletal growth, improves body composition and optimizes mental and motor development. GH treatment with doses normalising IGF1 in adults with PWS improves body composition and to some degree quality of life (QoL) and physical fitness. GH treatment is safe but glucose metabolism must be continuously monitored especially in obese patients and in patients with heredity for diabetes, in addition to monitoring serum IGF-I and sleep related breathing disorders.

Incomplete sexual development is frequently seen in PWS. The majority has clinical and laboratory measurements demonstrating hypogonadism, which can be of both primary gonadal and hypothalamic origin. Sex-steroid treatment might be beneficial. Fertility has not been reported in PWS men while five pregnancies have been reported in PWS women.

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

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

Conclusion

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

DOI: 10.1530/endoabs.37.S29.4

S29.5

Management of endocrine transition: type 1 diabetes

Christina Kanaka-Gantenbein
University of Athens Medical School, Athens, Greece.

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

DOI: 10.1530/endoabs.37.S29.5

Debate

How to manage hyponatraemia according to guidelines?

D1.1

Abstract unavailable.

DOI: 10.1530/endoabs.37.D1.1

D1.2

How to manage hyponatraemia according to guidelines? The USA perspective

Joseph Verbalis
Georgetown University, Washington, District of Columbia, USA.

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

DOI: 10.1530/endoabs.37.D1.2

Meet the Expert

MTE1

Abstract unavailable.

DOI: 10.1530/endoabs.37.MTE1

MTE2

Management of prolactinoma

Dominique Maiter
Department of Endocrinology, UCL Cliniques St Luc, UCL, Brussels, Belgium.

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

DOI: 10.1530/endoabs.37.MTE2

MTE3

Abstract unavailable.

DOI: 10.1530/endoabs.37.MTE3

MTE4

Management of thyroid eye disease

Georg Brabant[1] & Anja Eckstein[2]
[1]Experimental and Clinical Endocrinology, University of Lübeck, Lübeck, Germany; [2]Department Neuroophthalmology, Strabism and Oculoplasics, University Eye Hostpital Essen, Essen, Germany.

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

DOI: 10.1530/endoabs.37.MTE4

MTE5

Central precocious puberty: management and long-term outcome

Juliane Léger
[1]Université Paris Diderot, Paris, France; [2]Hôpital Robert Debré, Paris, France.

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

DOI: 10.1530/endoabs.37.MTE5

MTE6

Management of the transgender patient

Guy T'Sjoen
Ghent University Hospital, Ghent, Belgium.

Gender dysphoria (GD) is a condition in which a person experiences discongruency between their assigned sex and what they feel their genderidentity is. A person with gender dysphoria experiences persistently uncomfortable feelings about their birth gender (Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-V) (American Psychiatric Association).
During the 'real life experience' hormonal treatment usually starts and applicants are required to live socially in the desired gender role before irreversible surgical reassignment is considered. Cross sex hormonal treatment is desired by trans persons to help them successfully live as a member of their identified gender. It is

clear that both in adults and adolescents the decision for starting hormonal treatment is not to be made by the endocrinologist. The mental health professionals (psychiatrists and/or psychologists), by preference working in a multidisciplinary Gender team, will guide these persons to make an informed decision about hormonal treatment. Eligibility criteria and readiness as described by WPATH's Standards of Care-7th version, should be evaluated. The goal of treatment in female-to-male trans persons is to induce virilization and to stop menses. The prinicipal hormone treatment is a testosterone preparation. In male-to-female trans persons oestrogen and anti-androgen treatment is provided. Treatment regimens are currently not standardised and include various forms of oestrogens, progestins, and/or (anti-) androgens as reported by different clinical centres. So far, no randomized intervention trials are available so treatment is largely experience-based. Options for fertility preservation should be discussed with the clients before hormonal intervention.

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

Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Tangpricha V & Montori VM. Endocrine Society. *J Clin Endocrinol Metab* 2009 Sep; **94** (9): 3132–54.

Sexual and physical health after sex reassignment surgery. De Cuypere G, T'Sjoen G, Beerten R, Selvaggi G, De Sutter P, Hoebeke P, Monstrey S, Vansteenwegen A & Rubens R. *Arch Sex Behav* 2005 Dec; **34** (6): 679–90.

DOI: 10.1530/endoabs.37.MTE6

MTE7

Management of adrenal insufficiency

Stefanie Hahner
Department of Medicine I, Endocrinology and Diabetology, University Hospital Wuerzburg, Wuerzburg, Germany.

For a long time it has been assumed that patients with adrenal insufficiency (AI) can live without any restriction when receiving standard hormone replacement therapy.

However, recent evidence indicates that subjective health status (SHS) in patients with primary adrenal insufficiency is significantly impaired at least in a subgroup of patients and that mortality is increased compared to the general population.

The observation of impaired SHS holds true for patients with both primary and secondary AI and also for patients with congenital hyperplasia. It is reflected by a high proportion of occupational changes and restriction of leisure time activities. The non-physiological cortisol profile achieved by standard replacement strategies has been particularly claimed as main cause for the reduced SHS but also lack of further hormones like DHEA and epinephrine might be an underlying cause. Recent efforts aim at improving replacement strategies by mimicking a more physiological cortisol profile and to restore androgen deficiency and new therapeutic options have emerged.

The observation of increased mortality has led to more detailed studies demonstrating that adrenal insufficiency per se represents one of the most common causes of death in this patient population but also death from infectious disease and cardiovascular disease appears to be increased. Adrenal crisis is more frequent than suggested by earlier analyses, even in well educated patients. Both physical and psychological distress may precipitate adrenal crisis with infectious disease being the most frequent precipitating factor. The relative risk to die from infectious disease is largely increased, suggesting that many of these patients are not sufficiently treated resulting in adrenal crisis. Recent activities aim at an improved and standardized patient education and an improvement of awareness in health professionals.

In conclusion both, replacement strategies in chronic AI and prevention and treatment of adrenal crisis deserve particular attention and need to be further improved.

DOI: 10.1530/endoabs.37.MTE7

MTE8

Acromegaly and cancer

Cesar Boguszewski
Sempr Fed Univ Parana, Curitiba, Brazil.

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

DOI: 10.1530/endoabs.37.MTE8

MTE9

Management of craniopharyngioma

Rachel Crowley
Beaumont Hospital, Dublin, Republic of Ireland.

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

DOI: 10.1530/endoabs.37.MTE9

MTE10

Approach to the patient with dyslipidaemia

Alper Sonmez
Gulhane Military Medical Academy, Department of Endocrinology and Metabolism, Ankara, Turkey.

In clinical practice, dyslipidaemia defines the elevated plasma total cholesterol, LDL cholesterol or triglycerides or the decreased HDL cholesterol levels. In recent years however, new laboratory methods helped us understand that the functions of lipoproteins are more important than their amounts. Dyslipidaemia is one of the most important and correctable risk factors for the atherosclerotic cardiovascular diseases (CVD). The epidemiological data recurrently show a very significant linear relationship between the elevated cholesterol levels and the risk of CVD. Genetic background and age are the two major predictors of serum cholesterol levels. In the developed countries, with a considerable amount elderly people, more than half of the population have increased total cholesterol levels. Other important determinants of serum cholesterol and triglycerides are the eating habits and the presence of regular physical activity. The risk of dyslipidaemia is significantly increased in the modern populations with high caloric intake and low exercise capacity. The main problem with dyslipidaemia is the fact that it is mostly an asymptomatic metabolic disorder. Therefore, it is crucial for the primary care physicians to know when, where and how to search for and how to manage the patient with dyslipidaemia.

In a patient with dyslipidaemia, the medical history should be taken for the possible diseases or drugs, which may cause secondary dyslipidaemia. A family history of premature atherosclerosis is crucial as it may help us recognize familial dyslipidaemias. Also, the lifestyle of the patient, including history of smoking or alcohol intake and exercise habits should carefully be sought. Also, the presence of effort angina, dyspnoea or claudication intermittence should be searched in the systemic examination of the patient. In the physical examination, the body mass index and arterial blood pressures should be measured and the peripheral pulses should be checked. Also the eye and cutaneous findings of dyslipidaemia should

be searched during the physical examination. In order to rule out the secondary causes, fasting glucose levels, liver enzymes, creatine, urinary protein excretion and TSH levels should be seen in the laboratory evaluation process.

DOI: 10.1530/endoabs.37.MTE10

MTE11

MTE 13: management of male osteoporosis

Dilek Gogas Yavuz
Department of Endocrinology and Metabolism, Marmara University School of Medicine, Istanbul, Turkey.

Osteoporosis in men is recently recognized as a major underestimated public health problem. In 2050, the incidence of hip fracture in men is expected to increase by 310% worldwide. After the age of 50, one out of three osteoporotic fractures are seen in men. Men suffering any major fracture have a higher mortality rate than women osteoporotic fractures. Screening is usually recommended in many guidelines above the age of 65 or 70 years and those younger aged with risk for osteoporosis. However, its relevance requires validation through prospective studies.

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

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

DOI: 10.1530/endoabs.37.MTE11

MTE12

Medullary thyroid cancer

Thera P Links
Department of Endocrinology, University Medical Center Groningen, Groningen, The Netherlands.

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

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

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

Tumour progression can be predicted by calcitonin and CEA doubling times and also ^{18}F-FDG-PET and ^{18}F-DOPA-PET are useful in guiding therapeutic steps in patients with MTC. The treatment for MTC is still a topic of discussion. American guidelines recommend total thyroidectomy, level VI and ipsilateral level II–V lymph node dissection when nodal involvement is suspected, while the British guidelines advocate bilateral selective lymph node dissection in T2–4 tumours or palpable lymph nodes in level VI and II–V. For metastatic disease local treatment options (radiofrequency ablation, radiotherapy) are available. Tyrosinekinase inhibitors show encouraging results, however no benefits on overall survival have yet been demonstrated.Several other different strategies for the treatment of MTC are currently being considered, many of which target downstream proteins of RET.

DOI: 10.1530/endoabs.37.MTE12

MTE13

Abstract unavailable.

DOI: 10.1530/endoabs.37.MTE13

MTE14

Meet the expert 17 (MTE17): management of Turner syndrome

Aneta Gawlik
Department of Pediatrics, Pediatric Endocrinology and Diabetes, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland.

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

DOI: 10.1530/endoabs.37.MTE14

MTE15

Primary hyperparathyroidism (Meet-the-Expert 18)

Alper Gürlek
Department of Endocrinology and Metabolism, Faculty of medicine, Hacettepe University, Ankara, Turkey.

Primary hyperparathyroidism (PHPT) is the third common disorder of the endocrine system. It reaches a peak incidence between ages 50–60. Biochemical screening has increased its incidence up to one per 1000 (USA), and most cases are presented with asymptomatic mild hypercalcemia. The most common cause in affected individuals is a functioning single parathyroid adenoma. In advanced cases, bones (brown tumours, osteitis fibrosa cystica) and the kidney (nephrolithiasis, nephrocalcinosis) as well as many organ systems may be affected by hyperparathyroidism and associated hypercalcemia. Concomitant vitamin D deficiency might mask hypercalcemia and if remains untreated, may exacerbate postoperative hungry bone syndrome and hypocalcemia.The biochemical diagnosis basicly depends on demonstration of elevated or inappropriately normal serum parathyroid hormone concentrations in a hypercalcemic patient. Guidelines for the management of asymptomatic hyperparathyroidism has been revised in recent years, the latest being issued in 2014. Based on these criteria, a patient with asymptomatic PHPT should be given to surgery if he/she fulfils one of the following: i) serum calcium exceeding 1.0 mg/dl (0.25 mmol/l) above the upper limit of normal range, ii). BMD by DXA:*T*-score < -2.5 at lumbar spine, total hip, femoral neck or distal 1/3 radius, iii) vertebral fracture by X-ray, CT, MRI or vertebral fracture assessment (VFA) iv)creatinine clearance <60 cc/min, v) 24 h urinefor calcium >400 mg/day and increased stone risk by chemical analysis, vi) presence of nephrolithiasis or

nwphrocalcinosis by X-ray, USG or CT, vii) age <50. The minimally invasive approach has recently gained popularity for parathyroidectomy. Various imaging techniques may be used to preoperatively localise the adenomas such as Tc99m-sestamibi SPECT CT, CT scan, MRI and ultrasonography. Intraoperative assessment of PTH is very useful to determine the success of such surgery. Patients who refuse or who are not good candidates for surgery may be followed by calcimimetic agent cinacalcet which is useful to reduce serum calcium level. Bisphosphonates are in widely used for patients in an attempt to increase BMD and reduce the risk of fragility fracture. If there is no intention to reduce calcium or increase BMD, the patient may be followed without any medication.

DOI: 10.1530/endoabs.37.MTE15

MTE16

Assessing osteoporosis in the young adult

S Faisal Ahmed
University of Glasgow, Glasgow, UK.

Fragility fractures in the young individual are an uncommon clinical scenario and when faced with such a situation, appropriate assessment is required to ensure correct diagnosis of the underlying aetiology and to avoid unnecessary interventions. Although, primary causes of osteoporosis such as osteogenesis imperfecta are considered rare, this group of conditions has considerable phenotypic and genotypic heterogeneity and may be underdiagnosed. However, the majority of the young people with fragility fractures have a secondary cause as the underlying aetiology. This may include a range of chronic diseases and medications that can impact on bone turnover, modelling or bone mineral homeostasis. Given the increasing prevalence of young adults with childhood-onset chronic disease, it is likely that a higher number of people with such conditions will require an assessment of bone health in early adulthood. The diagnosis of osteoporosis in the young adult remains contentious. In growing children, interpretation of results and changes need to take into account the differences in stature, growth and pubertal development as well as the poor evidence that exists in this population for DXA BMD as a predictor of fractures. The ISCD recommends that people up to the age of 19 years should not be diagnosed with osteoporosis solely based on low BMD by DXA and has placed a greater focus on the presence of pathological fractures, especially vertebral, such that the diagnosis of vertebral fractures alone is indicative of osteoporosis in the younger individual regardless of DXA parameters. A stronger emphasis on vertebral morphometry, is therefore, becoming more routine in the assessment of osteoporosis. With technological advances in imaging as well as greater availability in the health care sector, it is also possible that identification of osteoporosis will reduce its reliance on techniques such as DXA in favour of other modalities that can provide a 'virtual bone biopsy' such as high resolution MRI or CT.

Disclosure
The Medical Fund of the University of Glasgow
The Chief Scientist Office of Scotland
The Government of Libya.

DOI: 10.1530/endoabs.37.MTE16

MTE17

Abstract unavailable.

DOI: 10.1530/endoabs.37.MTE17

Educational Workshop

Practical publishing advice

EW1.1

Abstract unavailable.

DOI: 10.1530/endoabs.37.EW1.1

EW1.2

The peer review process

Jens Mittag
University of Lübeck, Lübeck, Germany.

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

DOI: 10.1530/endoabs.37.EW1.2

EW1.3

Publishing ethics: fabrication, falsification and plagiarism

Chris McCabe
University of Birmingham, Birmingham, UK.

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

DOI: 10.1530/endoabs.37.EW1.3

EW1.4

Responding to reviewer comments

Johannes Romijn
AMC, University of Amsterdam, Amsterdam, The Netherlands.

A statement attributed to Aristotle is: 'You can easily avoid criticism by saying nothing, doing nothing, and being nothing.' If you want to do research, apply for competitive grants and publish relevant scientific papers in competitive journals, criticism is a fact of life. There is also a positive twist to criticism: it is a major driving force to advance knowledge in science.

Frequently, the first reaction of authors to critical comments of reviewers is anger. Nonetheless, most reviewers involved in the review process are reasonable. They are intermediates between the authors and the editors. The authors like to publish in high ranking journals and the editors aim to accept papers with the highest potential for citations. In this respect authors and editors depend on each other.

In many cases the criticisms can be predicted in advance. Weaknesses in objectives, study design, methods, analyses, data acquisition, interpretation of results will frequently be identified by the reviewers. To prevent these comments, the authors should aim for high quality research from the start of the study. Ultimately, the comments of the reviewers frequently enable to improve the manuscript. It is important to address these comments in an elegant constructive way, precisely answering each comment in detail.

DOI: 10.1530/endoabs.37.EW1.4

EW1.5

Open access

Jens Sandahl Christiansen
MEA, Aarhus University Hospital, Aarhus, Denmark.

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

DOI: 10.1530/endoabs.37.EW1.5

EW1.6

Abstract unavailable.

DOI: 10.1530/endoabs.37.EW1.6

European Young Endocrinologists

Sex, drugs and rocking hormones

EYES1.1

Abstract unavailable.

DOI: 10.1530/endoabs.37.EYES1.1

EYES1.2

Abstract unavailable.

DOI: 10.1530/endoabs.37.EYES1.2

EYES1.3

Drug addiction and the endocannabinoid system

Miriam Melis
Department of Biomedical Sciences, University of Cagliari, Monserrato CA, Italy.

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

DOI: 10.1530/endoabs.37.EYES1.3

EYES1.4

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

Bojana Popovic[1], Dejana Popovic[2], Djuro Macut[1], Ivana Bozic Antic[1], Tamara Bogavac[1], Tatjana Isailovic[1], Valentina Elezovic[1], Sanja Ognjanovic[1], Dusan Ilic[1], Jadranka Antic[1], Milan Petakov[1] & Svetozar Damjanovic[1]
[1]Clinic for Endocrinology, Diabetes, and Metabolic Diseases, Clinical Centre of Serbia, Belgrade, Serbia; [2]Clinic for Cardiology, Clinical Centre of Serbia, Belgrade, Serbia.

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

DOI: 10.1530/endoabs.37.EYES1.4

EYES1.5

Abstract unavailable.

DOI: 10.1530/endoabs.37.EYES1.5

EYES1.6

Abstract unavailable.

DOI: 10.1530/endoabs.37.EYES1.6

Endocrine Nursing

The journey of the patient with obesity: multidisciplinary care approach

EN1.1

Abstract unavailable.

DOI: 10.1530/endoabs.37.EN1.1

EN1.2

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

Carel le Roux
UCD, Dublin, Ireland.

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

DOI: 10.1530/endoabs.37.EN1.2

EN1.3

Abstract unavailable.

DOI: 10.1530/endoabs.37.EN1.3

Professional development, poster presentations and networking

EN2.1

Abstract unavailable.

DOI: 10.1530/endoabs.37.EN2.1

EN2.2

Challenges in diagnosis, treating and managing patients presenting with hyponatraemia, polydipsia and polyuria: implications for nursing practice

Anne Marland[1] & Philip Yeo[2]
[1]Oxford University Trust Hospitals, Oxford, UK; [2]The London Clinic, London, UK.

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

DOI: 10.1530/endoabs.37.EN2.2

EN2.3

Developing an effective abstract and poster presentation

Margaret Keil
NIH-NICHD, Bethesda, Maryland, USA.

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

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

DOI: 10.1530/endoabs.37.EN2.3

EN2.4

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

Andrew Dwyer
University Hospital Lausanne (CHUV), Lausanne, Switzerland.

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

Disclosure
COST Action BM1105, Endocrine Nurses Society.

DOI: 10.1530/endoabs.37.EN2.4

EN2.5

Abstract unavailable.

DOI: 10.1530/endoabs.37.EN2.5

EN2.6

Abstract unavailable.

DOI: 10.1530/endoabs.37.EN2.6

Meet the Nurse Expert

EN3.1

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

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

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

DOI: 10.1530/endoabs.37.EN3.1

EN3.2

Abstract unavailable.

DOI: 10.1530/endoabs.37.EN2.5

EN3.3

Abstract unavailable.

DOI: 10.1530/endoabs.37.EN3.3

Oral Communications

Adrenal 1

OC1.1

PRKACA defects and cortisol-producing lesions of the adrenal cortex: specific clinical phenotypes and histological features

Anna Angelousi[1], Paraskevi Salpea[1], Fabio Faucz[1], Michail Zilbermint[1], Edra London[1], Rossella Libe[2], Stephanie Espiard[2], Charalampos Lyssikatos[1], Fahrettin Kelestimur[3], Electron Kebebew[4], Brigitte Delemer[5], Sylvie Hieronimus[6], Bruno Feve[7], Gerald Raverot[8], Jerome Bertherat[2] & Constantine Stratakis[1]
[1]Endocrinology and Genetics Branch, NICHD, Bethesda, USA; [2]INSERM, Endocrinology Branch, Hôpital Cochin, Paris, France; [3]ERCIYES, Department of Endocrinology, Kayseri, Turkey; [4]Endocrine Oncology Branch, National Institutes of Health (NIH), Bethesda, USA; [5]Department of Endocrinology, CHU Reims, Reims, France; [6]Department of Endocrinology, CHU Nice, Nice, France; [7]Department of Endocrinology, CHU St-Antoine, Paris, France; [8]Department of Endocrinology, CHU Lyon, Lyon, France.

Introduction
Germline inactivating mutations of the protein kinase A (PKA) regulatory subunit RIα (the *PRKAR1A* gene) cause primary pigmented nodular adrenocortical disease (PPNAD); other cyclic AMP (cAMP) signalling defects have been associated with bilateral adrenocortical hyperplasia (BAH), cortisol-producing adenoma (CPA) and related lesions. Recently, *PRKACA* somatic mutations were detected in single, sporadic CPAs in approximately 40% of patients with ACTH-independent Cushing syndrome (AICS) whereas germline copy-number gain (CNG) of the 19p13 *PRKACA*-locus was associated with micronodular BAH (iMAD) and PPNAD.
Methods
We studied 68 patients with AICS, 24 patients with CPA and 44 patients with BAH that did not have known germline *PRKAR1A* defects. The clinical characteristics of the patients were evaluated with genetic analysis.
Results
The hotspot somatic mutation (p.Leu206Arg, c.617T>G) in the *PRKACA* gene was identified in 3 of 25 CPAs. Ten of 44 patients with BAH had germline CNGat the 19p13 *PRKACA*-locus. In one of these cases, AICS with combined androgen production due to a PPNAD-like BAH that became clinically apparent during pregnancy, there was familial inheritance of the 19p13 CNG, which segregated with AICS in the affected members. There were specific dexamethasone-responses and histological features of the patients with somatic PRKACA defects; BAH due to 19p13 CNG was mostly micronodular but was not consistently PPNAD-like.
Conclusions
We conclude that both germline and somatic *PRKACA* defects are associated with specific clinical and histologic phenotypes. Their recognition may help in the earlier identification of these patients with AICS and in the case of hereditary BAH, the earlier recognition of carriers with 19p13 CNG may result in better patient outcome.
Disclosure
This research was supported in part by the Intramural Research Program of the National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development (Clinical trial registration number: NCT00005927).

DOI: 10.1530/endoabs.37.OC1.1

OC1.2

Functional study of ARMC5 (armadillo repeat containing 5), a new tumour suppressor gene involved in primary bilateral macronodular adrenal hyperplasia

ludivine Drougat[1], Stéphanie Espiard[1], Stéphane Doly[1], Stéphanie Rodriguez[1], Marthe Rizk-Rabin[1], Rossella Libé[1,2], Guillaume Assié[1,2], Stefano Marullo[1], Bruno Ragazzon[1] & Jérôme Bertherat[1,2]
[1]Institut Cochin, Université Paris Descartes, CNRS (UMR 8104)- Inserm, U1016, PARIS, France; [2]AP-HP, Hôpital Cochin, Department of Endocrinology, Center for rare adrenal diseases, PARIS, France.

Introduction
Primary bilateral macronodular adrenal hyperplasia (PBMAH) are adrenocortical tumors leading to adrenal Cushing's syndrome. Recently, our laboratory has identified the first gene predisposing frequently to PBMAH in adults, named ARMC5 (Armadillo Repeat Containing 5)1. The ARMC5-inactivating mutations identified in leucocyte and tumour DNA in PBMAH patients suggest that ARMC5 is a tumour suppressor gene. However, the mechanisms of action of ARMC5 remain unknown. The aim of this work is to understand both the biological role of ARMC5 protein and how mutations alter this function.
Methods
The human adrenocortical cells H295R were transiently transfected with expression vectors of WT or mutants ARMC5. The eight mutations studied (F700del, C657R, I664S, L754P, Y736S, R362L, R315W, L331P, C139R) have been identified in leukocyte or tumour DNA of operated PBMAH patients. After 8 and 14 h of transfection, apoptosis was analysed by flow cytometry and immunofluorescence analysis (cleaved caspase 3 staining). In parallel, co-immunoprecipitation experiments were carried out to identify partners of the ARMC5 protein by mass spectrometry.
Results
Cell overexpressing WT ARMC5 promptly undergo apoptosis compared to cells transfected with mutants ARMC5 that all lose the ability to induce apoptosis. We identified, by mass spectrometry, 16 proteins specifically interacting with WT ARMC5. These proteins are involved in the degradation of proteins, the redox system and the cAMP/PKA pathway including subunits of PKA. The interaction between ARMC5 and subunits of PKA were then confirmed by co-immunoprecipitations and BRET (Bioluminescence Resonance Energy Transfert) experiments.
Conclusion
These results confirm the role of ARMC5 in the regulation of apoptosis and the loss of this function by the mutants identified in PBMAH. By its binding with actors involved in the cAMP/PKA pathway, known to play an essential role in the adrenocortical function, ARMC5 seems to be a major factor in the adrenal cortex physiology and pathophysiology. 1- Assié et al., NEJM, 2014.
Disclosure
This study was supported in part by the Agence Nationale de la Recherche (ANR-10-Blan-1136), the COMETE Network (Programme Hospitalier de Recherche Clinique Grant AOM95201), the Assistance Publique-Hôpitaux de Paris.

DOI: 10.1530/endoabs.37.OC1.2

OC1.3

[$^{123/131}$I] azetidinylamide a novel radiotracer for diagnosis and treatment of adrenocortical tumours – from bench to bedside

Stefanie Hahner[1], Britta Heinze[1], Ken Herrmann[2], Andreas K Buck[2], Christina Blümel[2], Heribert Hänscheid[2], Joachim Brumberg[2], David Michelmann[1], Lukas Nannen[1], Martin Ries[1], Martin Fassnacht[1], Bruno Allolio[1] & Andreas Schirbel[2]
[1]University Hospital Wuerzburg, Dept of Medicine I, Endocrinology and Diabetology, Wuerzburg, Germany; [2]University Hospital Wuerzburg, Dept. of Nuclear Medicine, Wuerzburg, Germany.

Background
We have recently introduced [$^{123/131}$I]iodometomidate (IMTO) which selectively binds to the adrenocortical enzymes aldosterone synthase and 11ß-hydroxylase as SPECT tracer. IMTO has been proven to be useful for molecular adrenal imaging and radiotherapy in adrenal cancer (ACC). As IMTO is rapidly inactivated by endogenous esterases which may impair target tissue to background activity and therapeutic efficacy, >50 new IMTO derivatives have been designed and tested. For the new compound [$^{123/131}$I] azetidinylamide (IMAZA), comparable inhibition of CYP11B enzyme activity and a higher metabolic stability after incubation with liver microsomes was proven *in vitro* compared to IMTO.
Methods
IMAZA was subsequently analysed regarding its intracellular uptake in NCI-h295 cells and binding to mitochondrial membranes. *In vivo* biodistribution of [^{125}I] IMAZA was investigated in CD1 mice. Toxicity testing did not show toxic side effects at standard doses. In four patients with advanced ACC [^{123}I]MAZA or [^{131}I] MAZA was used for diagnostic evaluation of radiotherapy as a treatment option on a compassionate use basis and in three patients dosimetry and therapy was performed. Blood levels of tracer and metabolites were determined by radio-HPLC.
Results
In comparison to [^{125}I]IMTO, [^{125}I]IMAZA demonstrated higher uptake in adrenocortical cells and higher accumulation in the mitochondrial subfraction. In biodistribution experiments in CD1 mice, [^{125}I]IMAZA showed a higher, more selective and longer lasting adrenal uptake compared to [^{125}I]IMTO *in vivo*. Accordingly, first clinical data show higher metabolic stability in vivo with rapid clearance of unbound tracer. This significantly improved target to background ratios for [$^{123/131}$I]IMAZA resulting in highly improved imaging quality and calculated tumour doses up to 180 Gy in treated patients.
Conclusion
[$^{123/131}$I]azetidinylamide is a highly promising radiotracer for molecular adrenal imaging and radiotherapy of adrenocortical carcinoma. The highly specific and lasting uptake in the target tissue lead to superior imaging quality and therapeutic potential compared to IMTO.

Disclosure
This work was supported by the IZKF Wuerzburg (Grant no. F124) and by the Else Kröner-Fesenius Stiftung (Grant no. 2010_EKES.29 and Grant no. 2013_A213).
DOI: 10.1530/endoabs.37.OC1.3

OC1.4

^{11}C-metomidate PET-CT in primary aldosteronism: five possible indications for a non-invasive alternative to adrenal vein sampling

Andrew S Powlson[1], Olympia Koulouri[1], Elena Azizan[2], Carmela Maniero[2], Kevin Taylor[3], Franklin Aigbirhio[4], Brendan Koo[5], Heok K Cheow[6], John Buscombe[6], Mark Gurnell[1] & Morris J Brown[2]
[1]Metabolic Research Laboratories, Institute of Metabolic Science, University of Cambridge, Cambridge, UK; [2]Clinical Pharmacology Unit, University of Cambridge, Cambridge, UK; [3]Department of Clinical Biochemistry, University of Cambridge, Cambridge, UK; [4]Wolfson Brain Imaging Centre, University of Cambridge, Cambridge, UK; [5]Department of Radiology, Addenbrooke's Hospital, Cambridge, UK; [6]Department of Nuclear Medicine, Addenbrooke's Hospital, Cambridge, UK.

Background
Adrenal vein sampling (AVS) remains the gold-standard for distinguishing unilateral and bilateral disease in primary aldosteronism (PA). However, it is invasive, technically demanding, and may yield inconclusive or equivocal results. ^{11}C-Metomidate PET-CT (^{11}C-MTO-PET-CT) is a non-invasive alternative to AVS for localising unilateral aldosterone-producing adenomas (APAs).
Methods/patients
We report a retrospective analysis of 61 sequential patients with PA referred for ^{11}C-MTO-PET-CT in the three years since our original study (Burton *et al*., JCEM 2012). All had a definite/possible adenoma on previous CT/MRI *or* AVS suggesting lateralisation.
Results
^{11}C-MTO-PET-CT was unequivocally positive leading to a recommendation for surgery in 26/61 patients (42.6%). In all 12 cases operated locally to date (unilateral adrenalectomy), adrenocortical histology and CYP11B2 immunopositivity was confirmed, with biochemical cure of PA (normalisation of the aldosterone-to-renin ratio); six patients await adrenalectomy. In a further eight 'tertiary' referrals from elsewhere, lateralisation by ^{11}C-MTO-PET-CT led to a recommendation for adrenalectomy, but clinical outcome data is awaited. Finally, where multiple nodules co-existed, ^{11}C-MTO-PET-CT accurately identified the causative tumour (confirmed by cell-culture, gene-expression and genotyping).
Discussion
The 26 patients in whom unilateral disease was confirmed had one of five indications for ^{11}C-MTO-PET-CT: i) AVS technically unsuccessful (failure to cannulate one of the adrenal veins); ii) technically adequate AVS, but without clear lateralisation; iii) AVS not possible (unable to safely withdraw spironolactone or epleronone); iv) no clear-cut abnormality on cross-sectional imaging; and v) patient choice not to undergo AVS. ^{11}C-MTO-PET-CT was also valuable in providing strong evidence against lateralisation, especially in patients with a definite unilateral adenoma on CT/MRI, but no resolution by AVS. In conclusion, analysis of ^{11}C-MTO-PET-CT in 61 sequential patients supports its use as an adjunct/non-invasive alternative to AVS. In addition, we speculate that ^{11}C-MTO-PET-CT may facilitate non-surgical targeted nodule-specific ablation or selective surgical adenomectomy when multiple nodules are present.

DOI: 10.1530/endoabs.37.OC1.4

OC1.5

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

Misu Lee[1,3], Iina Laitinen[2], Rickmer Braren[2] & Natalia S Pellegata[1]
[1]Helmholtz Zentrum München, Neuherberg, Germany; [2]Technische Universität München, Munich, Germany; [3]Yonsei University, Seoul, South Korea.

Currently, no effective medical therapy exists for inoperable phaeochromocytomas (PCCs). Thus, we investigated the antitumor potential of the dual PI3K/mTOR inhibitor NVP-BEZ235 against PCC *in vivo*. We employed a spontaneous model of endogenous aggressive PCCs (MENX rats), which closely recapitulate the human tumours. Administration of NVP-BEZ235 to MENX rats for 14 days inhibited proliferation (assessed by Ki67, NuSAP staining), vascularity (CD31, VEGFA), and induced apoptosis (active caspase 3) of PCCs *in vivo*. Diffusion weighted magnetic resonance imaging (DW-MRI) with calculated mean apparent diffusion coefficient (ADC) values pre- and post-therapy were determined and used as surrogate markers of tumour cellularity. ADC values were significantly increased after drug treatment ($P=0.0208$), further supporting a cytotoxic role of NVP-BEZ235 in PCC. Gene expression profiling (by RT-PCR arrays) of tumours from drug-treated and vehicle-treated rats showed that NVP-BEZ235 affects the expression of genes involved in cell death and survival, cell proliferation and motility. Among the genes down-regulated in NVP-BEZ235-treated vs vehicle-treated rat tumours was *Scl6a2,* encoding the norepinephrine transporter (NET), a common target of positron emitted tomography (PET) imaging of PCC. Specifically, we observed a dose-dependent reduction of both *Slc6a2* (by TaqMan) and NET (by immunohistochemistry) expression in rat PCCs following NVP-BEZ235 administration, which associated with decreased uptake of the radiolabeled norepinephrine analogue 18F-LMI1195 *in vivo*. To assess the relationship between NET levels and response to NVP-BEZ235, we generated a drug-resistant derivative of the MPC (mouse PCC) cell line. While incubation with NVP-BEZ235 reduced NET expression in MPC cells, no reduction was observed in the resistant derivative cells. This suggests that decreased NET expression associates with the ability of PCC cells to respond to PI3K/mTOR inhibition. Altogether, our data demonstrate that targeting PI3K/mTOR signalling is effective against PCCs and suggest that NET levels may represent a surrogate marker of therapy response to PI3K/mTOR inhibitors, which can be monitored by functional PET imaging.

Disclosure
This work was supported by SFB824, subproject B08, from the Deutsche Forschungs-gemeinschaft (DFG).
DOI: 10.1530/endoabs.37.OC1.5

Reproduction

OC2.1

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

Bao Hui Lee[1,2], Huey Min Tan[1], Yu Li[1], Zhiwei Zhang[1], Inthrani Raja Indran[1], Jun Li[1] & Eu Leong Yong[1]
[1]National University of Singapore, Obstetrics & Gynaecology, Singapore, Singapore; [2]National University of Singapore, NUS Graduate School for Integrative Sciences & Engineering, Singapore, Singapore.

Background
Polycystic Ovary Syndrome (PCOS) is an endocrine disorder characterized by hyperandrogenism in women, with a high incidence of insulin resistance. Decanoic acid (DA), a naturally occurring 10-carbon fatty acid, has been shown to improve insulin sensitivity and lipid profile in an *in vivo* model of diabetes without the induction of weight gain. However, the effects of DA on androgen production has not been explored.
Aim
The objective of this study was to evaluate the effects of DA on androgen production and regulation of steroidogenic enzymes *in vitro*and *in vivo*.
Methods
NCI-H295R human adrenocortical cells were used to assess the effects of DA on androgen production, gene and protein expression of the steroidogenic enzymes. In addition, an *in vivo* letrozole-induced PCOS rat model was used to assess if oral administration of glyceryl tridecanoate (GT), the triglyceride form of DA, may restore normal androgen production and alleviate the symptoms associated with PCOS.
Results
Our findings demonstrate that DA significantly inhibits gene and protein expression of HSD3B2, and androgen production in NCI-H295R cells in a dose-dependent manner. Notably, oral feed of the letrozole-induced PCOS rats with GT restored estrous cyclicity, reduced serum testosterone, and lowered fasting insulin.
Conclusion
Put together, this study has identified a natural compound, DA, as a promising drug candidate for the modulation of androgen biosynthesis. The inhibition of androgen biosynthesis by DA occurs, at least in part, via the suppression of HSD3B2, which codes for an essential enzyme in the steroidogenesis pathway. These results lay the platform for the development of DA for the management of hyperandrogenism and insulin resistance in PCOS.

Disclosure
This study was supported by a grant from the Singapore National Medical Research Council (NMRC/BnB/0007c/2013).
DOI: 10.1530/endoabs.37.OC2.1

OC2.2

Lipid accumulation product as a surrogate marker of metabolic syndrome in different phenotypes of polycystic ovary syndrome

Djuro Macut[1], Ivana Bozic Antic[1], Jelica Bjekic-Macut[2], Danijela Vojnovic Milutinovic[3], Dusan Ilic[1], Bojana Popovic[1], Tamara Bogavac[1], Biljana Kastratovic-Kotlica[4], Olivera Stanojlovic[5], Tatjana Isailovic[1], Valentina Elezovic[1], Sanja Ognjanovic[1], Milan Petakov[1] & Svetozar Damjanovic[1]

[1]Clinic of Endocrinology, Diabetes and Metabolic Diseases and Faculty of Medicine, University of Belgrade, Belgrade, Serbia; [2]CHC Bezanijska kosa, Belgrade, Serbia; [3]IBISS, University of Belgrade, Belgrade, Serbia; [4]Clinic of Gynecology and Obstetrics, and Faculty of Medicine, University of Belgrade, Belgrade, Serbia; [5]Institute of Physiology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia.

Introduction

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

Methods

We evaluated 365 PCOS women (PCOS: $25.05 \pm 6.24 - \text{kg/m}^2$; 25.48 ± 5.21 years) diagnosed using ESHRE/ASRM criteria and 125 BMI-matched healthy women (controls: 25.41 ± 5.16 kg/m^2; 30.35 ± 5.62 years). PCOS group was divided into four phenotypes: a (anovulation (ANOV), hyperandrogenism (HA), polycystic ovary morphology (PCOM)), B (ANOV, HA), C (HA, PCOM) and D (ANOV, PCOM). MetS was defined according to NCEP ATP III definition. LAP was calculated using formula ((WC-58)$\times$triglycerides). ROC curve analysis was performed to determine associations of LAP and MetS.

Results

The prevalence of MetS in phenotypes/controls was as following: A: 20.8%, B: 27.5%, C: 17.5%, D: 5.3%, and in Controls: 6.4%. Phenotype D and Controls had lower ($P<0.05$) MetS prevalence than all other PCOS phenotypes. LAP was significantly lower ($P<0.05$) in phenotype D (19.11 ± 25.51) and Controls (25.33 ± 23.17) than in all other phenotypes (A: 35.37 ± 41.29, B: 48.74 ± 47.70, C: 32.55 ± 38.11). ROC curve analysis indentified LAP cut off value of 25.94 to be the most preferable for predicting MetS in PCOS by NCEP ATP III criteria (AUC$=0.95 \pm 0.01$ (95% CI 0.93–0.97), sensitivity: 98.5%, specificity: 76.1%). This cut off value had higher negative than positive predictive value for the whole PCOS group (99.5% vs 52%, respectively) and also for the phenotypes (A: 100% vs 54%; B: 100% vs 58%; C: 98% vs 48%; D: 100% vs 33%).

Conclusion

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

DOI: 10.1530/endoabs.37.OC2.2

OC2.3

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

Olayiwola Oduwole[1], Hellevi Peltoketo[2], Ariel Poliandri[3], Laura Vengadabady[4] & Ilpo Huhtaniemi[1,5,]

[1]Imperial College London, London, UK; [2]Biocenter Oulu, University of Oulu, Oulu, Finland; [3]Queen Mary University of London, London; UK; [4]GlaxoSmithKline, London, UK; [5]University of Turku, Turku, Finland.

The gonadotropic hormones, LH and FSH are critical regulators of normal sexual functions including steroidogenesis and gametogenesis. Their essential role is underscored by the development of various hypogonadal phenotypes arising from genetic mutations. Constitutive activation of their cognate receptors also disturbs their function. We earlier showed that transgenic expression of an activating mouse *Fshr* mutant (*mFSHR*^{D580H}) in granulosa cells, under the anti-Müllerian hormone promoter, distorts ovarian function. Contrarily, transgenic males expressing this mutant in Sertoli cells were largely normal. To study further whether amplified FSH action affects spermatogenesis, we crossed the transgenic *Fshr* mutant males with Lhr deficient knockout (*Lhr*$^{-/-}$) mice, the homozygotes of which present with hypogonadism and infertility. The phenotype of the female litters from the crossbreeds largely mimicked those of *Lhr*$^{-/-}$ females. However, the double-mutant males presented with rescue of fertility, with normal testes size and spermatogenesis, and partially recovered seminal vesicles, but with delayed puberty, reflecting incomplete rescue of testosterone production. On attainment of full sexual maturity these mice sired litters similar to the wild-type (WT) littermates. Histologically, the testes of the adult mice partly mimicked those of *Lhr*$^{-/-}$ male mice with total absence of discernible Leydig cells in the interstitial space. In contrast, the seminiferous tubuli had normal diameter with full spermatogenesis. As expected, the Fshr, a Sertoli cell marker was upregulated in these mice, while the Leydig cell-specific genes, including Lhr and some key steroidogenic enzymes, were downregulated. Interestingly, treatment of these mice with the antiandrogen, flutamide had no effect on spermatogenesis, whereas it completely blocked spermatogenesis in the WT controls. Our findings demonstrate that excessive Fshr activation, in the absence of LH-stimulated Leydig cell function, and even without testosterone action, is able to restore and maintain spermatogenesis.

Disclosure

This work was supported by the Wellcome Trust Programme, grant 082101/Z/07/Z, the MRC, grant 060002 and the ESE short-term fellowship.

DOI: 10.1530/endoabs.37.OC2.3

OC2.4

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

Leen Antonio[1,3], Frederic Wu[4], Terrence O'Neill[5], Stephen Pye[6], Emma Carter[4], Joseph Finn[4], Michaël Laurent[2,6], Ilpo Huhtaniemi[7], Martin Rutter[4,8], Giulia Rastrelli[9], Gianni Forti[9], Gyorgy Bartfai[10], Felipe Casanueva[11], Krzysztof Kula[12], Margus Punab[13], Aleksander Giwercman[14], Frank Claessens[2], Brigitte Decallonne[13] & Dirk Vanderschueren[1,3]

[1]Department of Clinical and Experimental Medicine, Laboratory of Clinical and Experimental Endocrinology, KULeuven, Leuven, Belgium; [2]Department of Cellular and Molecular Medicine, Laboratory of Molecular Endocrinology, KULeuven, Leuven, Belgium; [3]Department of Endocrinology, University Hospitals Leuven, Leuven, Belgium; [4]Andrology Research Unit, Centre for Endocrinology & Diabetes, Institute of Human Development, The University of Manchester, Manchester, UK; [5]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, UK; [6]Department of Clinical and Experimental Medicine, Division of Gerontology and Geriatrics, KULeuven, Leuven, Belgium; [7]Institute of Reproductive and Developmental Biology, Department of Surgery and Cancer, Imperial College London, London, UK; [8]Manchester Diabetes Centre, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK; [9]Andrology Unit, Department of Clinical Physiopathology, University of Florence, Florence, Italy; [10]Department of Obstetrics, Gynaecology and Andrology, Albert Szent-Gyorgy Medical University, Szeged, Hungary; [11]Department of Medicine, Santiago de Compostela University, Complejo Hospitalario Universitario de Santiago (CHUS); CIBER de Fisiopatología Obesidad y Nutricion, Santiago de Compostela, Spain; [12]Department of Andrology and Reproductive Endocrinology, Medical University of LodZ, Lodz, Poland; [13]Andrology Unit, United Laboratories of Tartu University Clinics, Tartu, Finland; [14]Reproductive Medicine Centre, Malmö University Hospital, University of Lund, Lund, Sweden.

Background

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

Methods

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

Results

2540 men had normal TT (18.4 ± 5.5 (mean$\pm$S.D.) nmol/l) and FT (326 ± 75 pmol/l). There were 261 men in group 1 (normal TT (14.2 ± 3.7 nmol/l), low FT (195 ± 22 pmol/l)) and 92 men in group 2 (low TT (9.6 ± 0.7 nmol/l), normal FT (247 ± 20 pmol/l)).

Compared to referent, men in group 1 were older and had higher SHBG, whereas group 2 was younger and had lower SHBG. BMI was higher in both groups. Men in group 1, but not group 2, were in poorer health and had lower haemoglobin. Regression analysis showed that men in group 1 had less frequent morning erections ($P=0.012$), more erectile dysfunction ($P<0.001$) and more physical symptoms (limited vigorous activity ($P=0.011$), walking 1 km ($P=0.026$) and bending ($P=0.005$)). Compared to referent, sexual and physical symptoms did not differ in group 2.

Conclusions
Independent of age, BMI and comorbidities, men with isolated low FT, but normal TT, have more androgen deficiency-related symptoms than men with normal TT and FT levels; whereas symptoms do not differ in men with isolated low TT. Not only total, but also FT levels should therefore be assessed in men with hypogonadal symptoms.
Disclosure
The European Male Ageing Study is funded by the Commission of the European Communities Fifth Framework Programme 'Quality of Life and Management of Living Resources' Grant QLK6-CT-2001-00258.
DOI: 10.1530/endoabs.37.OC2.4

OC2.5

Bisphenol A-induced epithelial-mesenchymal transition was reversed with a phytoestrogen, genistein via oestrogen receptor and downregulation of transforming growth factor-beta signalling pathway

Ye-Seul Kim, Kyung-A Hwang & Kyung-Chul Choi
Laboratory of Biochemistry and Immunology, College of Veterinary Medicine, Chungbuk National University, Cheongju, Chungbuk, Republic of Korea.

Epithelial–mesenchymal transition (EMT) is an important process appeared in tumour migration or progression, which is activated by 17β-estradiol (E_2). As a typical endocrine disrupting chemical (EDC), bisphenol A (BPA) has a potential to promote EMT and migration of oestrogen responsive cancers. On the contrary, genistein (GEN) as a phytoestrogen is known to have chemopreventive effects in diverse cancers. In the present study, the effects of BPA and GEN on EMT and migration of BG-1 ovarian cancer cells and the underlying mechanism were investigated. ICI 182,780, an oestrogen receptor (ER) antagonist, was co-treated with E_2 or BPA to BG-1 cells to identify the relevance of ER signalling in EMT and migration. As results, E_2 and BPA upregulated the protein expression of vimentin, cathepsin D, and MMP-2, but downregulated the protein expression of E-cadherin via ER signalling, suggesting that E_2 and BPA promoted EMT and cell migration related gene expressions. However, the increased protein expression of Vimentin, Cathepsin D, and MMP-2 by E_2 or BPA was reduced by the co-treatment of GEN. In a scratch assay, the migration capability of BG-1 cells was enhanced by E_2 and BPA via ER signalling pathway, but reversed by the co-treatment of GEN. In the protein expression of SnoN and Smad3, E_2 and BPA upregulated SnoN, a negative regulator of TGF-β signalling, and downregulated Smad3, a transcription factor in the downstream pathway of TGF-β signalling, suggesting that E_2 and BPA simultaneously lead the downregulation of TGF-β signalling in the process of induction of EMT and migration of BG-1 cells via ER signalling. On the other hand, the co-treatment of GEN reversed the down-regulation of TGF-β signalling by E_2 and BPA. Taken together, GEN suppressed EMT and migration capacities of BG-1 ovarian cancer cells enhanced by E_2 and BPA via ER signalling and the downregulation of TGF-β signalling.
Disclosure
This work was also supported by a grant from the Next-Generation BioGreen 21 Program (no. PJ009599), Rural Development Administration, Republic of Korea.
DOI: 10.1530/endoabs.37.OC2.5

Calcium, vitamin D and bone

OC3.1

Effect of GNAS transcript manipulation on human mesenchymal stem cells differentiation towards osteocyte cell lineage: insight into the pathophysiology of ectopic ossification in GNAS-related disorders

Francesca Marta Elli[1,2], Valentina Boldrin[1,2], Valentina Parazzi[3], Enrico Ragni[3], Paolo Bordogna[1,2], Anna Spada[1,2], Lorenza Lazzari[3] & Giovanna Mantovani[1,2]
[1]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, U.O.C. Endocrinology, Milano, Italy; [2]Unità di Endocrinologia e Scienze Metaboliche, Dipartimento di Scienze Cliniche e di Comunità, Università degli Studi di Milano, Milano, Italy; [3]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Cell factory, Unit for Cellular Therapy and Cryobiology, Milano, Italy.

Epi/genetic defects at the imprinted GNAS locus, that encodes the α subunit of the stimulatory G protein (Gsα), have been associated with a heterogeneous group of rare diseases, termed as Pseudohypoparathyroidism. Most GNAS-based disorders have the common feature of episodic *de novo* formation of heterotopic ossifications (HO) in subcutaneous tissues. The mosaic tissue distribution of HO suggests that pathogenesis involves an abnormal differentiation of precursor cells, and that GNAS defects provide a sensitized background, but the molecular mechanism is still under investigation. To date, investigations have been mainly conducted in mouse models, thus we have developed an *in vitro* human model from surgically removed samples of subcutaneous fat (adipose-derived mesenchymal stem cells, ADMSCs) to study the determinants underlying HO formation in GNAS-related diseases. The multilineage differentiation ability of ADMSCs was confirmed via biochemical assays, specific stainings and expression analysis of specific markers. We also determined the preservation of GNAS imprinting profile during cell culture and handling. Subsequently, cells were treated with siRNAs against Gsα-specific or non-specific GNAS transcripts, the efficiency of transfection (ranging from about 75% at day 4, up to about 50% at day 21) was evaluated, as well as the effect on cell differentiation toward osteoblasts. No significant differences due to different siRNA target sequences were observed. The increase of alkaline phosphatase activity reflected cell maturation and non-induced silenced cells displayed an intermediate phenotype between cells grown in control and inducing medium (Abs 405 nm at day 14: silenced $= 0.507 \pm 0.16$, control $= 0.076 \pm 0.01$, induced $= 0.861 \pm 0.13$, $P < 0.05$). Moreover, Gsα-deficient cells, although not able to completely differentiate and depose mineralized matrix, began to lay down few, interspersed and very small calcium deposits. Future experiments will expand our knowledge in molecular mechanisms underlying HO formation in GNAS-related disorders, in order to test pharmacological treatments against HO formation and progression.
DOI: 10.1530/endoabs.37.OC3.1

OC3.2

The association of sclerostin serum levels with sclerostin expression in bone

Nathalie Bravenboer, Ruben Visser, Dirk Jan Mons, Angela Oostlander, Eveline Sohl, Hub van Essen, Renate de Jongh, Paul Lips, Annemieke Heijboer & Martin den Heijer
VU Medical Center, Amsterdam, The Netherlands.

Sclerostin is a major negative regulator of osteoblastic activity at tissue level. Serum sclerostin levels have been associated with bone mineral density and increased fracture risk. However, the relation between serum levels and expression on tissue levels is unknown. The aim of this study was to investigate this relationship. We used serum samples and bone biopsies from 26 patients that were available from a large randomised clinical trial, investigating with the effect of risedronate in patients with Crohn's disease and osteopenia (registered as NTR-163 Dutch Trial Register). Sclerostin expression in bone was detected using immunohistochemistry (mouse-human antibody, R&D systems). In cortical bone, sclerostin positive area was measured as a percentage from the total cortical area (NIS elements, Nikon). In trabecular bone, sclerostin expression is detected as number of positively stained osteocytes. Serum concentrations were determined by an enzyme-linked immunosorbent assay (Mesoscale discovery). We also assessed bone mineral density of the hip and lumbar spine with DEXA. Serum sclerostin was associated with the number of sclerostin positive trabecular osteocytes ($R = 0.54$, $P = 0.004$) but not with sclerostin positive area in cortical bone ($R = 0.07$, $P = 0.73$). Serum sclerostin levels and sclerostin expression in cortical bone as well as in trabecular bone showed positive correlations with bone mineral density of the spine. ($R = 0.55$, $P = 0.001$; $R = 0.38$, $P = 0.02$; $R = 0.35$, $P = 0.03$). With bone mineral density of the hip only the sclerostin positive area in cortical bone showed a correlation of 0.54 ($P = 0.0004$). We demonstrated that sclerostin levels in serum reflect the expression of sclerostin by osteocytes mostly in trabecular bone. Sclerostin expression in bone as well as sclerostin levels in serum are associated to bone mineral density, especially of the lumbar spine.
Disclosure
The study was supported by Amgen.
DOI: 10.1530/endoabs.37.OC3.2

OC3.3

Klotho expression in long bones is critical for FGF23 production during renal failure

Jovana Kaludjerovic[1], Hirotaka Komaba[1], Tadatoshi Sato[1], Takenobu Ishii[1], Hannes Olauson[2], Tobias Larsson[2] & Beate Lanske[1]
[1]Harvard School of Dental Medicine, Boston, Massachusetts, USA; [2]Karolinska Institutet, Stockholm, Sweden.

Klotho (KL) is a type-I-membrane protein required for FGF23 to bind FGFR1 and modulate mineral ion homeostasis. Loss of either KL or FGF23 results in severe mineralisation defects. We recently found that membrane KL is expressed in osteoblasts and osteocytes, which are major sites of FGF23 syntheses. To investigate the role of bone-specific KL in mineral ion homeostasis and the progression of bone mineralisation defects in chronic kidney disease, we generated a mouse strain with limb-specific KL deletion using Prx1-Cre. No differences were seen in body weight, serum phosphate, FGF23, PTH, calcitriol or cortical bone volume between $KL^{fl/fl}$ and $Prx1\text{-}Cre;KL^{fl/fl}$ mice at 6, 16 or 24 weeks of age. However, as early as 6 weeks of age $Prx1\text{-}Cre;KL^{fl/fl}$ mice had lower trabecular bone volume and connectivity than $KL^{fl/fl}$ mice. To challenge the mice, we induced chronic kidney failure by feeding mice adenine diet for 8 weeks. At 16 weeks of age, all mice fed adenine diet had reduced body weight, kidney atrophy, high urea concentrations (80–120 pg/ml) and hyperphosphataemia, confirming the induction of renal failure. No differences in these parameters were seen between adenine fed $KL^{fl/fl}$ and $Prx1\text{-}Cre;KL^{fl/fl}$ mice. However, limbs of adenine fed $Prx1\text{-}Cre;KL^{fl/fl}$ mice did not respond with an increase in *Fgf23* mRNA expression that is characteristic of renal failure and was observed in adenine fed $KL^{fl/fl}$ mice. As such, adenine fed $Prx1\text{-}Cre;KL^{fl/fl}$ had significantly lower serum iFGF23 levels than adenine fed $KL^{fl/fl}$ mice, higher expression of renal 1α-hydroxylase, hypercalcaemia and severe kyphosis. To validate the results, findings were confirmed in 5/6 NTX $Prx1\text{-}Cre;KL^{fl/fl}$ mice. Therefore, our data is the first to show that limb-specific KL plays an important role in regulating mineral ion homeostasis and more importantly FGF23 production. This novel data suggests that Klotho expression in bone cells provides a sensor for the need of FGF23.

Disclosure
Dod – Department of Defense (PR120411).
Canadian Institutes of Health Research Postdoctoral Fellowship.
DOI: 10.1530/endoabs.37.OC3.3

OC3.4

Cardiovascular risk factors in patients with medically observed and operated primary hyperparathyroidism

Sevgi Çolak[1], Berna Imge Aydogan[2], Asena Gökçay Canpolat[2], Cansin Tulunay Kaya[3], Mustafa Sahin[2], Demet Çorapçioglu[2], Ali Riza Uysal[2] & Rifat Emral[2]
[1]Department of Internal Medicine, Faculty of Medicine, Ankara University, Ankara, Turkey; [2]Department of Endocrinology and Metabolism, Faculty of Medicine, Ankara University, Ankara, Turkey; [3]Department of Cardiology, Faculty of Medicine, Ankara University, Ankara, Turkey.

Introduction
It is known that patients with primary hyperparathyroidism (PHPT) have an increased cardiovascular morbidity and mortality. In our study, we aimed to investigate the cardiovascular risk factors in medically observed and operated PHPT patients.
Materials and methods
Twenty-nine medically observed (group A), 25 pre-operative (group B) and 23 post-operative (group C) patients with PHPT and 26 normocalcemic patients as control group (group D) were included to this study. Groups were assessed for flow mediated dilatation (FMD), carotid intima media thickness (CIMT), serum levels of sCD40L, hs-CRP and IL-8. Twelve patients with low levels of 25-hydroxy vitamin D (25OHD) in the medical treatment group were assessed in terms of these measurements before and 3 months after vitamin D replacement.
Results
Median FMD was 5, 5.1, 7.6 and 7.7% in groups A, B, C and D respectively. FMD measurement of group A was detected significantly lower than group C and D ($P=0.02$) and was similar with group B. FMD measurements of group B were also detected lower than group C and D but this did not reach to statistical significance. Results of CIMT measurement, serum sCD40L, IL-8 and hs-CRP levels showed no significant difference between groups. In 12 patients with low 25OHD within group A, FMD was increased to an average of 6.7% from 4.4% after vitamin D replacement ($P=0.04$).
Discussion
Endothelium-dependent vasodilatation was impaired in PHPT patients, particularly in medically treatment group, compared to control group. Vitamin D supplementation provide improvement in FMD measurements in medically followed PHPT patients with low 25OHD levels. The information that vitamin D replacement makes an improvement in endothelial dysfunction in PHPT patients with low 25OHD is a new contribution to the literature of our study.

Disclosure
This work was supported by 'Foundation of Ankara University Faculty of Medicine'.
DOI: 10.1530/endoabs.37.OC3.4

OC3.5

Three-year safety and efficacy data for recombinant human parathyroid hormone, rhPTH(1-84), in the treatment of adults with hypoparathyroidism: the RACE study

Bart L Clarke[1], Michael Mannstadt[2], Tamara J Vokes[3], Jeffrey Rothman[4], Mark L Warren[5], Douglas S Denham[6], Michael A Levine[7], Hjalmar Lagast[8], John P Bilezikian[9] & Dolores M Shoback[10]
[1]Mayo Clinic Division of Endocrinology, Diabetes, Metabolism, & Nutrition, Rochester, Minnesota, USA; [2]Endocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA; [3]Section of Endocrinology, University of Chicago Medicine, Chicago, Illinois, USA; [4]Division of Endocrinology, Staten Island University Hospital, Staten Island, New York, USA; [5]Endocrinology and Metabolism, Physicians East, PA, Greenville, North Carolina, USA; [6]Clinical Trials of Texas, Inc., San Antonio, Texas, USA; [7]Division of Endocrinology and Diabetes, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; [8]NPS Pharmaceuticals, Inc., Bedminster, New Jersey, USA; [9]Division of Endocrinology, College of Physicians and Surgeons, Columbia University, New York, New York, USA; [10]Endocrine Research Unit, SF Department of Veterans Affairs Medical Center, University of California, San Francisco, California, USA.

Hypoparathyroidism is a rare endocrine deficiency due to inadequate amounts of parathyroid hormone (PTH) and is characterised by hypocalcaemia and hyperphosphataemia. Current management regimens with large amounts of oral calcium and active vitamin D do not adequately control mineral homeostasis and can lead to complications in many patients. The phase III REPLACE and RELAY clinical trials established the efficacy and safety of once-daily s.c. injection of recombinant human PTH, rhPTH(1-84). Here we present 3-year data from RACE, the open-label extension of REPLACE and RELAY. Patients received 25 or 50 μg/day rhPTH(1-84) with up-titration to 50, 75, or 100 μg/day if active vitamin D and oral calcium could be further reduced and serum calcium level remained at or above optimised baseline. Of 49 patients enrolled at 12 US centres (mean age 48 ± 10 years; 82% women; mean hypoparathyroidism duration 16 ± 12 years), 38 (78%) completed 36 months of rhPTH(1-84) as of September 30, 2014. 50% of patients (18/36) met the efficacy endpoint ($\geqq$50% reduction in oral calcium (or $\leq$500 mg/day), $\geqq$50% reduction in active vitamin D dose (or $\leq$0.25 μg/day), and albumin-corrected serum calcium $\geqq$1.87 mmol/l). Mean calcium and calcitriol doses were 2194 ± 1732 mg/day and 0.7 ± 0.4 μg/day, respectively, at baseline, and fell to 803 ± 1259 mg/day (–54%$\pm$80%) and 0.2 ± 0.3 μg/day ($-71\%\pm39\%$), respectively, at month 36. Albumin-corrected serum calcium levels were maintained (2.1 ± 0.2 mmol/l at both baseline and month 36). Serum phosphorus levels were uniformly lower than baseline (1.56 ± 0.19 mmol/l): mean change was -0.22 ± 0.29 mmol/l at month 36. Adverse events (AEs) were reported by 48 (98%) patients; most common AEs were hypocalcemia (35%), muscle spasms (29%), and nausea (27%). Serious AEs occurred in 9 (18%) patients; none were considered to be treatment related. This extension trial confirms the efficacy and safety of rhPTH(1-84) for an extended 3-year period.

Disclosure
Yes. This work was supported by NPS Pharmaceuticals, Inc.
DOI: 10.1530/endoabs.37.OC3.5

Diabetes

OC4.1

Novel glucagon receptor antagonist peptides improve glycaemic control and partially protect against streptozotocin induced diabetes in mice

Finbarr O'Harte[1], Laura McShane[1,2] & Nigel Irwin[1]
[1]University of Ulster, Coleraine, N. Ireland, UK; [2]University of Central Lancashire, Lancashire, UK.

Glucagon receptor KO mice are resistant to the clinical manifestations of diabetes induced by streptozotocin (STZ) and retain normal glycaemic control and glucose tolerance. In the present study the effects of chronic (18 days) once daily i.p. administration of two different glucagon receptor antagonists (GRA); desHis[1]Pro[4]Glu[9]-glucagon (GRA-1) and its related acylated peptide desHis[1]Pro[4]Glu[9](Lys[12]PAL)-glucagon (GRA-2) were investigated in groups of male ($n=8$) high fat fed (45% fat) STZ-induced (125 mg/kg) diabetic mice. Food intake, body weight, blood glucose and plasma insulin were measured at regular intervals. At the end of the study period an oral glucose tolerance test, insulin sensitivity test and analysis of metabolic rate was performed. Terminal plasma glucagon concentrations and pancreatic insulin content were also measured. GRA-1 and GRA-2 showed no significant improvement in STZ-induced weight loss over the course of the study, however both peptides delayed STZ-induced glucose elevations ($P<0.05$) on day 3. No significant differences were found in non-fasting blood glucose on day 18 between the STZ-treated and both GRA treated groups. In comparison to STZ-treated controls (Area under curve $AUC_{0\text{-}60min}$ 749.5 ± 152.8): GRA-1 (530.2 ± 188.6) and GRA-2 (510.9 ± 184.9) significantly ($P<0.05$) improved oral glucose tolerance in STZ-induced diabetes, producing a 30% reduction in the overall glucose excursion. Both GRA-1 and GRA-2 significantly ($P<0.05$) enhanced the hypoglycaemic effects of insulin by 1.36-fold (Area above curve $AAC_{0\text{-}60min}$ 1471 ± 144.6) and 1.29-fold (1396 ± 112.8), compared with STZ-treated controls (1079 ± 165.5). Energy expenditure was also significantly increased ($P<0.001$) in both GRA treatment groups compared with STZ-treated controls. GRA-2 significantly enhanced ($P<0.001$) pancreatic insulin content (0.85 μg/g tissue) versus STZ-treated controls (0.02 μg/g; $P<0.001$). In conclusion, novel glucagon receptor antagonist peptides improved glycaemic control and partially protected against STZ-induced type 1 diabetes in mice.

Disclosure
Proof of Concept (PoC106) funding from Invest NI.
DEL PhD Studentship award.

DOI: 10.1530/endoabs.37.OC4.1

OC4.2

Complement factor 5 deficiency leads to defective insulin receptor processing and severe systemic insulin resistance

Takuya Kikuchi, Dario A Gutierrez, Emily K Anderson-Baucum, W Reid Bolus, Merla J Hubler, Brian T Palmisano, Owen P McGuinness & Alyssa H Hasty
Vanderbilt University, Nashville, Tennessee, USA.

Activation of complement factor 5 (C5) produces the anaphylatoxin C5a and the proinflammatory cytolytic complex C5b-9. Recent studies have shown that C5a receptor (C5aR) deficiency leads to improved systemic and white adipose tissue (WAT) insulin sensitivity. This phenotype is considered to be due to the potent inflammatory potential of signalling through C5aR; however, the pleiotropic functions of C5 in inflammation and metabolism remain to be elucidated. We investigated the effect of C5 itself on systemic glucose tolerance and insulin sensitivity and found C5 to play a critical role in metabolic health. To determine the metabolic phenotype of C5 deficiency, we performed glucose tolerance tests and hyperinsulinaemic euglycaemic clamps using C5 deficient (C5D) and C5 sufficient (C5S) mice. Surprisingly, we found that C5D mice developed severe glucose intolerance and insulin resistance compared to C5S controls. Glucose uptake in muscle and WAT was lower in C5D mice. Conversely, C5S mice injected with C5a adenovirus showed improved insulin sensitivity and increased glucose uptake in muscle and WAT. We next sought to determine the mechanism for insulin resistance in C5D mice. We showed that expression and glycosylation of insulin receptor (InsR) was impaired in the liver, muscle, and WAT of C5D mice. Consequently, AKT phosphorylation following insulin stimulation was decreased in the liver of C5D mice. Insulin resistance in C5D mice was independent of obesity, inflammation, and leukocyte infiltration into WAT or liver. We tested the effect of C5 siRNA on HepG2 liver cells, which resulted in decreased total InsR protein levels and decreased insulin-stimulated AKT phosphorylation. Cumulatively, these results reveal a novel function of C5 on glucose tolerance and insulin sensitivity via InsR processing that is independent of immune cell infiltration, inflammation, and/or obesity.

Disclosure
This project was supported by a Mouse Metabolic Phenotyping Center MICROmouse award to AHH (5U24 DK076169).

DOI: 10.1530/endoabs.37.OC4.2

OC4.3

Chronic, long-term administration of Vardenafil improves endothelial function and corrects hypogonadism in patients with type 2 diabetes mellitus. A longitudinal, prospective, randomized, placebo-controlled, double blind, clinical trial

Daniele Santi[1,2], Alessandro Guidi[2], Antonio Granata[2], Elisa Pignatti[3], Roberto Bozic[5], Stefano Zaza[6], Laura Roli[4], Tommaso Trenti[4], Cesare Carani[1] & Manuela Simoni[1,2]
[1]Unit of Endocrinology, Department of Biomedical, Metabolic and Neural Sciences University of Modena and Reggio Emilia, Modena, Italy; [2]Azienda USL of Modena, Modena, Italy; [3]Center for Genomic Research University of Modena and Reggio Emilia, Modena, Italy; [4]Laboratory of clinical pathology and endocrinology, Azienda USL of Modena, Modena, Italy; [5]PerkinElmer, Milan, Italy; [6]LCMS Product Specialist. SHIMADZU Italia, Milan, Italy.

Background
Endothelial dysfunction leads to cardiovascular complications in type 2 diabetes mellitus (T2DM), through a reduction of nitric oxide (NO)-mediated relaxation. Phosphodiesterase-5 inhibitors (PDE5i) have hemodynamic effects, improving NO levels.
Aim
To investigate if long term, chronic treatment with the PDE5i Vardenafil improves systemic endothelial function in men with T2DM.
Methods
A longitudinal, prospective, investigator-started, randomized, placebo-controlled, double-blind, clinical-trial was carried out. 54 male patients affected by T2DM diagnosed within the last 5 years were enrolled. 26 and 28 patients were assigned by permuted block randomization to the verum and placebo-group, respectively. The study consisted of an enrollment phase, a treatment phase (24 weeks) (Vardenafil/placebo 10 mg twice-daily), and a follow-up phase (24 weeks). Parameters evaluated: International Index of Erectile Function (IIEF)-15, flow mediated dilation (FMD), intima media thickness (IMT), routine hematologic analyses. Serum testosterone (T) and its precursors were measured by liquid-chromatography tandem mass-spectrometry (LC-MS/MS). Gonadotropins were evaluated by ELISA.
Results
Only one serious adverse event was registered in the placebo group. The erectile function domain of IIEF-15 ($P=0.049$) improved after treatment. At the end of the treatment phase FMD significantly increased ($P=0.002$) while IMT ($P=0.003$), fibrinogen ($P=0.005$), white blood cells count ($P=0.018$) and Red cells Distribution Width ($P=0.028$) significantly decreased. FMD was significantly related to T serum levels ($P=0.002$), which significantly improved after Vardenafil treatment only in hypogonadal men ($T<10.4$ nmol/l) ($P=0.023$), without changes in gonadotropin serum levels. Smoking-habits, hypertension and glycemic control influenced the hemodynamic and inflammatory parameters.
Conclusions
This is the first double-blind, placebo-controlled clinical-trial in which T2DM men are chronically treated with Vardenafil for 6 months, and followed-up for 6 months after therapy-withdrawal. Chronically administered Vardenafil is safe and effective in T2DM patients and improves both tissue oxygenation and inflammatory markers, but this effect is lost after therapy withdrawal. For the first time, we demonstrate that chronic Vardenafil therapy improves T (measured by LC-MS/MS) in diabetic, hypogonadal men, an effect possibly due to improved microcirculation in the testis (EudraCT number 2009-014137-25).

DOI: 10.1530/endoabs.37.OC4.3

OC4.4

Islet stellate cell isolated from Goto-Kakizaki rats affects β-cell function

Zilin Sun[1], Fengfei Li[1,2], Bijun Chen[1], Ling Li[1], Min Zha[1], Wei Xu[1], Shaoxia Zhou[3] & M G Bachem[3]
[1]Department of Endocrinology, Zhongda Hospital, Institute of Diabetes, Medical School, Southeast University, Nanjing, China; [2]Department of Endocrinology, Nanjing First Hospital, Nanjing Medical University, Nanjing, China; [3]Department of Clinical Chemistry, University Hospital Ulm, Ulm, Germany.

Background
Evidence suggests that pancreatic stellate cells (PSCs) are present in intra-/peri-islets in type 2 diabetes mellitus (T2DM). We isolated stellate cell from islets (ISC) of Goto-Kakizaki (GK) rats. Given these cells are intra-islets, which possibly affect the biological behavior of β-cell. This study was designed to determine the effects of ISC isolated from fibrotic islets of GK rats on β-cell function and survival.
Methods
ISC was isolated from islets of GK rats using the outgrowth method. We determined the genome-wide digital gene expression (DGE) profiles of ISC by DGE technology. Insulin-producing β-cell line were treated with ISC supernatant (SN). Then, INS-1 cell proliferation, apoptosis, and insulin production were measured.
Results
ISC grew out from cultured GK rat islets, with a triangular shape and large nucleus. These cells expressed α-smooth muscle actin (α-SMA), vimentin, and desmin. ISC genes expression was significantly overlapped with that of PSC. We also observed 1067 genes differentially expressed in ISC compared with PSC. The 5-ethynyl-2′deoxyuridine-positive INS-1 cells treated with ISC-SN were significantly decreased compared with control. Propidium iodide (PI)-positive INS-1 cells in ISC-SN groups were 2.6-fold higher than those in control groups. Caspase-3 activity was associated with increased PI-positive cells. INS-1 cells cultured with ISC-SN were significantly reduced than that in control groups.
Conclusions
ISC presented in fibrotic islet of GK rats might be a special PSC, which impaired β-cell function, proliferation and increased β-cell apoptosis.
Disclosure
National Nature Science Foundation of China (nos 30971399, 81170716, and 81270010).
DOI: 10.1530/endoabs.37.OC4.4

OC4.5

Efficacy of mesenchymal stem cells transplantation on glycaemic profile in streptozotocin induced diabetic Wistar rat

Shobhit Bhansali, Vinod Kumar, Uma Nahar Saikia, Vivekanand Jha, Anil Bhansali & Pinaki Dutaa
PGIMER, Chandigarh, India.

Introduction
Bone marrow is an abundant source of adult stem cells that can differentiate into various cell types. Administration of mesenchymal stem cells (MSCs) in irradiated diabetic rat model has transiently shown to decrease blood glucose level. This study examines the effect of high dose and multiple injections of MSCs on glycaemic profile, their localisation and regeneration of islet in diabetic Wistar rat.
Methods
The study was carried out in male Wistar rats categorised into three groups ($n=6$, in each group); Group 1as control, group 2 STZ (50 mg/Kg) induced diabetic group and group 3 experimental group. 5-bromo-2-deoxyuridine (BrdU) labelled allogenic MSCs were injected in the non–irradiated diabetic rat of the experimental group through rat tail-vein. The blood glucose profile was subsequently monitored at regular intervals. Rats were sacrificed at day 45 and pancreas was examined for localization of BrdU labelled stem cells by immunofluorescence and islet-neogenesis by immunohistochemistry.
Results
There was a significant reduction in blood glucose level after administration of MSCs in the experimental group ($P<0.001$). The presence of BrdU labelled MSCs in islet suggested their localization in the pancreas. Co-expression of anti-BrdU and anti-insulin antibody indicated trans-differentiation/fusion into insulin producing cells evidenced by significant increase in total number of islet ($P=0.004$) and insulin positive cells ($P<0.0001$) in experimental group.
Conclusion
The MSCs administration in non-irradiated diabetic Wistar rat reduces hyperglycaemia and is accompanied by increased islet-neogenesis, possibly through trans- differentiation/fusion.
DOI: 10.1530/endoabs.37.OC4.5

Steroids, developmental and paediatric endocrinology

OC5.1

Maternal microbiota regulate glucocorticoids levels and placental development in mice

Maha Al-Asmakh[1,2], Lars Hedin[3] & Sven Pettersson[2]
[1]Qatar University, Doha, Qatar; [2]Karolinska Institute, Stockholm, Sweden; [3]Sidra Medical and Research Center, Doha, Qatar.

The gut microbiota contributes to postnatal development and maturation by influencing barrier functions of the intestinal wall, the development of the immune system, and the utilisation of nutrients. Recent studies have also implicated a role in the prenatal period since the maternal gut microbiota is altered during pregnancy with a potential role in the regulation of glucose homeostasis and protection against preterm birth. Using as a model system germ-free mice that have never encountered a live bacterium and pathogen-free mice that were reared in an environment free of monitored mouse pathogens, we demonstrated that lack of gut microbiota is associated with an altered hypothalamic-pituitary-adrenal axis (HPA) and impaired placental development. Germ-free (GF) mice displayed elevated serum glucocorticoids and reduced levels of glucocorticoid regulated insulin-like growth factor 2 (IGF2) and peroxisome proliferator-activated receptor (PPAR) β and γ compared to specific pathogen-free (SPF) dams, which correlated with an impairment of placenta development. Morphological analysis revealed reduced labyrinth size, inhibited vascularization and reduced expression of the tight junction proteins in the placenta from GF dams compared to SPF dams. Permeability test using a 1-kDa tracer showed an increased permeability in GF placental barrier. We conclude that the maternal microbiome can influence placental development and we propose that mammalian development, known to have the capacity to modulate placenta size and morphology to ensure the development of the growing offspring, is under the influence of the maternal microbiome, the forgotten organ.
Disclosure
This work was supported by grants from Qatar University, VR, Cancerfonden, EU-project TORNADO, and the Singapore Millennium Foundation.
DOI: 10.1530/endoabs.37.OC5.1

OC5.2

Vitamin D decreases *in vitro* glucocorticoid sensitivity via down regulation of glucocorticoid receptor expression

Narjes Nasiri Ansari[1], Eliana Spilioti[1], Vasiliki Kalotychou[2], Geena Dalagiorgou[1], Paraskevi Moutsatsou[1], Athanasios Papavassiliou[1] & Eva Kassi[1,2]
[1]Laboratory of Biochemistry, Medical School, National and Kapodistrian University of Athens, Athens, Greece; [2]National and Kapodistrian University of Athens, 1st Department of Internal Medicine, Medical School, Athens, Greece.

Introduction
Glucocorticoids (GCs) are used in the treatment of chronic inflammatory or autoimmune diseases. However, patients are often resistant to the GC effects. Response to GCs is triggered through glucocorticoid receptor (GR). An important regulator of GR activity is the *FKBP5*. FKBP5 binds to co-chaperones promoting a conformation with lower cortisol affinity. The number of GRs is another determinant of GC sensitivity; GR expression is regulated by the nuclear receptor co-repressor-1 (NCoR-1). An anti-inflammatory/immunomodulatory role of $1,25(OH)_2D_3$ has been demonstrated. We aimed to investigate the effect of $1,25(OH)_2D_3$ on the *in vitro* GC sensitivity.
Participants and methods
PBMCs were isolated from eight healthy women and incubated with dexamethasone for the last 48 h, with or without pre-incubation with $1,25(OH)_2D_3$ for 11 days. Co-incubation experiments with dexamethasone and $1,25(OH)_2D_3$ were also performed. *In vitro* GC sensitivity was assessed with dexamethasone-induced effects on GILZ mRNA expression (real-time PCR). FKBP5 and NCoR1 mRNA expression as well as GRα mRNA and protein expression (western blot analysis) were assessed. Intracellular distribution of GR was visualised by IF.

Results
After 11 days of culture, incubation of PBMCs with dexamethasone for the last 48-h resulted in 12-fold increase in GILZ-mRNA levels. When PBMCs were pre-incubated with $1,25(OH)_2D_3$, dexamethasone (last 48-h) induced a significant down-regulation of GILZ mRNA expression. When PBMCs were pre-treated with $1,25(OH)_2D_3$ for 11 days, dexamethasone (last 48-h) caused a significant down-regulation of GRα mRNA expression, confirmed at protein level. Treatment of PBMCs with $1,25(OH)_2D_3$, led to significant decrease in FKBP5 and NCoR1 mRNA levels. IF staining showed that vitamin D causes a GR translocation from nucleus to cytoplasm.
Conclusion
$1,25(OH)_2D_3$ decreased the *in vitro* glucocorticoid sensitivity in PBMCs isolated from healthy women. This effect is, at least in part, attributed to the reduction of GRα expression due to a mechanism that did not appear to implicate NCoR1 or FKBP5 expression. Moreover a $1,25(OH)_2D_3$-induced GR translocation from nucleus to cytoplasm is also involved. The mechanism through which vitamin D modulates response to glucocorticoids remains to be fully delineated.
Disclosure
General Secretariat for Research and Technology.
DOI: 10.1530/endoabs.37.OC5.2

OC5.3

Activators of AMP-activated protein kinase regulate adipocyte aldosterone secretion and mineralocorticoid receptor signalling
Anna White, Aurelie Nguyen Dinh Cat, Augusto Montezano, Ian Salt & Rhian Touyz
Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK.

The increasing global prevalence of obesity requires urgent intervention to limit the anticipated surge of associated cardiometabolic morbidity and mortality. The energy sensor AMP-activated protein kinase (AMPK) is one proposed target for treating metabolic disorders and is downregulated in adipose tissue of obese insulin resistant individuals. Given the strong relationship between metabolic syndrome and overactivity of the renin-angiotensin-aldosterone system (RAAS) we investigated the role of AMPK in regulating adipocyte RAAS and mineralocorticoid receptor (MR) signalling. In vitro studies were carried out using differentiated 3T3-L1 (mouse) and SW872 (human) adipocytes. AMPK activators AICAR (1 mM) and A769662 (300 μM) were applied for 8 or 24 h. RT-PCR, immunoblotting and ELISA were used to assess effects on components of the renin-angiotensin-aldosterone system. Angiotensinogen, angiotensin II type 2 receptor and mineralocorticoid receptor mRNA levels were upregulated in differentiated adipocytes compared to undifferentiated fibroblasts. Aldosterone secretion by 3T3-L1 adipocytes and SW872 adipocytes was increased by 8 h of incubation with AICAR or A769662 respectively. Expression of Steroidogenic Acute Regulatory (StAR) mRNA was upregulated in accordance with aldosterone secretion along with associated down-regulation of MR mRNA and protein. Furthermore, we examined downstream MR targets serum and glucocorticoid-regulated kinase 1 (SGK1) and Lipocalin 2 which were both upregulated despite decreased MR. Interestingly, cells which produced aldosterone in response to AMPK activators exhibited a severe down-regulation of AMPK protein levels by 24 h. These data suggest that AMPK acts to control RAAS activity in adipocytes. We hypothesise that prolonged AMPK hyperactivation *in vitro* results in AMPK depletion allowing aldosterone secretion with subsequent increase in MR signalling. The upregulation of RAAS previously reported in obesity may be partially explained by the downregulation of AMPK related to excess nutrition.
Disclosure
This work was supported by Diabetes UK.
DOI: 10.1530/endoabs.37.OC5.3

OC5.4

Adipose tissue-specific androgen generation fuels an adverse metabolic phenotype in patients with polycystic ovary syndrome
Michael O'Reilly[1], Punith Kempegowda[1], Laura Gathercole[2], Angela Taylor[1], Iwona Bujalska[1], Jeremy Tomlinson[2] & Wiebke Arlt[1]
[1]University of Birmingham, Birmingham, UK; [2]University of Oxford, Oxford, UK.

Insulin resistance and androgen excess are the cardinal features of polycystic ovary syndrome (PCOS). The severity of hyperandrogenism and metabolic dysfunction in PCOS are closely correlated, but underlying mechanisms remain poorly understood. Aldoketoreductase type 1C3 (*AKR1C3*) is an important source of adipose androgen generation, activating androstenedione to testosterone (T). We postulated that *AKR1C3* plays a critical role linking androgen metabolism and metabolic phenotype in PCOS.
We undertook *in vivo* deep phenotyping in ten women with PCOS and ten age/BMI-matched controls. Patients underwent oral challenge with 100mg of the androgen precursor dehydroepiandrosterone, with serum sampling every 30 min for 4 h and concomitant adipose microdialysis. Serum and adipose microdialysate androgens were measured by LC/MS. In complementary *ex vivo* and *in vivo* studies, we investigated adipose androgen generation, employing primary cultures of human adipocytes and the preadipocyte cell line SGBS. The impact of androgens upon adipose lipid metabolism was assessed through measurement of *de novo* lipogenesis, free fatty acid uptake (FFA) and β-oxidation.
After oral DHEA, area under the curve for serum T was higher in PCOS patients than controls, suggesting enhanced *AKR1C3* activity. 5α-dihydrotestosterone (DHT) was detectable in adipose interstitial fluid and was higher in PCOS than controls. Adipose interstitial glycerol levels were reduced in PCOS patients. Subcutaneous adipose *AKR1C3* mRNA expression correlated strongly with BMI. In human adipocytes, insulin up-regulated *AKR1C3* expression and activity, while T increased *de novo* lipogenesis; both T and DHT increased FFA uptake and suppressed β-oxidation.
Here we provide integrated *in vivo, ex vivo*, and *in vitro* evidence that hyperinsulinaemia may drive adipose androgen generation through increased *AKR1C3* expression and activity. This may have consequences for adipocyte function by driving lipid accumulation. Resultant adipocyte hypertrophy in PCOS could lead to increased insulin resistance, fuelling a vicious circle of hyperinsulinaemia, adipose androgen generation and increased lipid accumulation.
Disclosure
This work was supported by Wellcome Trust Clinical Research Training Fellowship (099909) to Dr Michael O'Reilly.
DOI: 10.1530/endoabs.37.OC5.4

OC5.5

Pituitary hormone secretion profiles in IGSF1 deficiency syndrome
Sjoerd Joustra[1], Ferdinand Roelfsema[1], Erik Endert[2], Bart Ballieux[1], Paul van Trotsenburg[2], Eric Fliers[2], Noortje Corssmit[1], Daniel Bernard[3], Wilma Oostdijk[1], Jan-Maarten Wit[1], Alberto Pereira[1] & Nienke Biermasz[1]
[1]Leiden University Medical Center, Leiden, The Netherlands; [2]Academic Medical Center, Amsterdam, The Netherlands; [3]McGill University, Montréal, Canada.

Context
Loss-of-function of immunoglobulin superfamily 1 (*IGSF1*) causes an X-linked syndrome of central hypothyroidism, macroorchidism, and variable prolactin deficiency, GH deficiency in childhood, delayed pubertal testosterone rise, and/or obesity. The clinical features advert towards a pivotal role for IGSF1 in the pituitary gland, but detailed knowledge on pituitary hormone secretion in this syndrome is lacking.
Objective
To study detailed 24 h spontaneous pituitary hormone secretion in patients with the IGSF1 deficiency syndrome.
Methods
We performed a 24 h sampling study with measurements every 10 min in eight IGSF1 deficient patients. Deconvolution, modified cosinor, and approximate entropy (ApEn) analyses were applied to quantify TSH, prolactin, and gonadotropin secretion rates, diurnal rhythmicity, and regularity of hormone release. Results were compared to matched healthy controls or (for TSH) patients with subclinical primary hypothyroidism (SCH).
Results
Compared to both healthy controls and SCH, IGSF1 deficient patients showed decreased pulsatile secretion of TSH with decreased disorderliness and absence of diurnal variation. Basal and pulsatile secretion of FSH was increased, while LH secretion was not different from healthy controls. For prolactin secretion, two phenotypes were observed, with absence of prolactin secretion in some and increased basal and total prolactin secretion in others.
Conclusion
The TSH secretion pattern is consistent with the previously proposed hypothesis of defective TRH signalling in IGSF1 deficiency, which is further supported by a decreased TSH response to TRH in patients, and the decreased expression of pituitary *Trhr* mRNA in *IGSF1* knock-out mice. However, the increased FSH and prolactin secretion, but normal LH secretion, in combination with the delayed puberty despite normal testicular growth, have been observed in untreated primary hypothyroidism, and provoke some novel hypotheses.
DOI: 10.1530/endoabs.37.OC5.5

Thyroid

OC6.1

3,5-T2 might play a crucial role in the rodent heart

Julika Lietzow[1], Priyavathi Dhandapani[1], Wenke Jonas[2] & Josef Köhrle[1]
[1]Institut für experimentelle Endokrinologie, Charité – Universitätsmedizin Berlin, Berlin, Germany; [2]Department of Experimental Diabetology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany.

The endogenous thyroid hormone metabolite 3,5-diiodothyronine (3,5-T2) has attracted attention as a metabolically active substance modulating metabolism via classical thyroid hormone (TH) receptor-dependent and rapid plasma membrane, cytosolic and mitochondrial signaling pathways. Accordingly, 3,5-T2 has been proposed as a potential hypolipidaemic agent without inducing thyromimetic effects and is frequently used as illicit weight-reducing agent. The objective of the present study was to investigate 3,5-T2 effects on energy and lipid metabolism in a mouse model of diet-induced obesity. Adult male mice received either 3,5-T2 (2.5 μg/g bw) or saline i.p. over 28 days. Contrary to our expectations the heart weight strongly increased by 26 percent with 3,5-T2 treatment. Because only limited data are currently available about 3,5-T2 effects on heart, we started to investigate the potential role of 3,5-T2 in cardiac remodeling and hypertrophy. The results in 3,5-T2 exposed heart tissue indicate that 3,5-T2 modulates expression of TH responsive cardiac genes. The gene expression of Ca^{++}-ATPase (*Serca2a2*) was significantly increased while protein and gene expression of the Ca^{++}-ATPase inhibitor phospholamban was decreased. Interestingly, 3,5-T2 application enhanced transcript concentration of myosin heavy chain β (*Myh7*) and of the brain natriuretic peptide (*Nppb*) and reduced the mRNA concentration of TH receptor alpha (*Thra*) indicating a potential role of 3,5-T2 in activation of a cardiac fetal gene program and involvement of non-classical TH signaling pathways. To understand the molecular basis and to identify possible mechanisms we used the cardiomyocyte cell line H9c2. LC-MS/MS data reveal a preferential uptake of 3,5-T2 compared to classical thyroid hormones. Moreover, first findings in differentiated cardiomyoblasts show that 3,5-T2 (100nM) increased the gene expression of Ca^{++}-ATPase and β-MHC comparable to the in vivo data. In conclusion, our results suggest that 3,5-T2 treatment in mice alters expression of cardiac genes and might exert profound possibly adverse cardiac and cardiovascular effects.

Disclosure
DFG grant KFO 218 TP3 KO 922-18/1.
DOI: 10.1530/endoabs.37.OC6.1

OC6.2

Biological activity of novel thyroid hormone analogues: role of Na+ taurocholate cotransporting polypeptide in liver selectivity

Giulia Brigante[1,2], Bo Carlsson[3], Simone Kersseboom[4], Robin P Peeters[4] & Theo J Visser[4]
[1]Unit of Endocrinology and Metabolism, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy; [2]Department of Medicine, Endocrinology and Metabolism and Geriatrics, Azienda AUSL of Modena, NOCSAE, Modena, Italy; [3]Karo Bio AB, Huddinge, Sweden; [4]Erasmus Medical Center, Rotterdam, The Netherlands.

Background
The interest in the potential effect of thyromimetics in lowering serum cholesterol is growing. Thyroid hormone actions on lipid metabolism are exerted in the liver and mediated by the T3 receptor TRβ1. The creation of molecules transported into hepatocytes by liver-specific transporters can increase the liver selectivity of thyromimetics. Sodium taurocholate co-transporting polypeptide (NTCP), a solute carrier protein primarily expressed on the basolateral membrane of hepatocytes, is particularly interesting.
Objectives
The role of NTCP in the liver preferential uptake of a series of new thyromimetics was analysed.
Methods
The compounds to test (KB141, KB5588, KB6628, KB6823, KB3488, KB3493, KB3495, KB4933, KB4956, KB5035, KB5160, KB5359, KB5525, KB5526, KB5866, KB6594, KB8038) were synthesised at Karo Bio AB. To explore the effect of NTCP on the nuclear availability of each compound, COS1 cells were co-transfected with TRβ1, NTCP, a construct coding for a TRE-dependent luciferase reporter and a control renilla reporter. Two days after transfection, cells were incubated for 24 h with 0.1–1000 nM of each compound. Incubation with the same concentrations of T3 was added as a control. The luciferase/renilla ratio was the measure of the compound transcriptional activity.
Results
Like T3, KB141, KB5588, KB3488 and KB6823 demonstrated no differences in transcriptional activity in the absence or presence of NTCP. KB6628, KB5035, KB5866, KB5160 and KB4956 showed a 1.5-fold higher activity in cells transfected with NTCP compared to cells transfected with empty pcDNA3 vector. KB3493, KB3495, KB5359, KB5525, KB5526, KB4933, KB6594 and KB8038 showed an even greater difference as they had no activity in the absence of NTCP and a fourfold higher activity in the presence of NTCP.
Conclusions
NTCP is an attractive transporter to target thyromimetics to the liver.

DOI: 10.1530/endoabs.37.OC6.2

OC6.3

Different TSH suppressive effects of liothyronine combination according to Thr92Ala type 2 deiodinase polymorphism

Dong Yeob Shin, Kwang Joon Kim, Jiyeon An & Eun Jig Lee
Division of Endocrinology and Metabolism, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea.

Introduction
Type 2 deiodinase (D2) catalyses intracellular T_3 production in several human tissues including pituitary gland, hence occupying an important role in the feedback regulation of TSH secretion. Although several previous researches have shown that Thr92Ala D2 polymorphism with decreased D2 enzymatic activity influences the levothyroxine dose requirement and the set point of the hypothalamus–pituitary–thyroid axis for postoperative TSH suppressive therapy in thyroid cancer patients, the clinical implications of D2 polymorphism and liothyronine replacement in thyroid cancer patients are still unknown.
Methods
The effect of liothyronine combination on TSH suppression according to Thr92Ala D2 polymorphism in 40 papillary thyroid cancer patients (20 males and 20 females; age 46.6±10.9 years, range 20–66) who were persistently unable to repress the serum TSH levels to less than 0.1 μIU/ml for at least 3 months despite the daily 2.0 μg/kg intake of levothyroxine were analysed. Total thyroidectomy with central compartment neck dissection and postoperative radioactive iodine ablation was performed in all patients at least a mean of 48.8±35.8 months before this study.
Results
In these patients, a decreased of mean TSH level was observed in all patients after 3 months of 12.5 μg liothyronine add on with 50 μg reduction of levothyroxine (3.18 vs 0.28 μIU/ml, $P=0.002$). After liothyronine combination, serum T_3 and free T_4 levels became more comparable to preoperative levels. Of the 40 patients, Ala/Ala homozygous genotype was observed in eight patients (20%), while WT and heterozygous type were observed in 15 (37.5%) and 17 (42.5%) patients, respectively. Preoperative serum free T_4 level was lower in Ala/Ala homozygous patients (0.98 vs 1.28 ng/dl, $P=0.006$). Ala/Ala homozygous patients displayed higher ratio of TSH level before and after liothyronine combination compared with patients carrying the Thr92 variant (X/Thr patients) (133.9±178.6 vs 25.5±41.5, $P=0.003$).
Conclusion
Thr92Ala D2 polymorphism is associated with liothyronine-dependent TSH suppressive intensity in athyreotic individuals. Thr92Ala D2 polymorphism analysis will be beneficial in predicting the effect of T_3 combination in thyroid cancer patients that are unable to achieve a full TSH suppression from levothyroxine mono-therapy.

DOI: 10.1530/endoabs.37.OC6.3

OC6.4

The usefulness of determining the presence of BRAF (V600E) mutation in fine needle aspiration cytology of thyroid nodules cells

Aldona Kowalska[1], Janusz Kopczynski[2], Artur Kowalik[3], Danuta Gasior-Perczak[1], Iwona Palyga[1], Katarzyna Lizis-Kolus[1], Dariusz Waligorski[1], Dorta Szyska-Skrobot[1], Agnieszka Walczyk[1], Stefan Hurej[1], Agnieszka Chil[2], Renata Chodurska[3], Malgorzata Chlopek[3], Elzbieta Wypiorkiewicz[3], Ewelina Nowak[3] & Stanislaw Gozdz[4]
[1]Department of Endocrinology, Kielce, Poland; [2]Department of Neoplasm Pathology, Kielce, Poland; [3]Department of Molecular Diagnostics, Kielce, Poland; [4]Chemotherapy Clinic, Kielce, Poland.

Introduction
Fine needle aspiration cytology (FNACC) is the basic tool used in the diagnosis of thyroid cancer (TC) in nodular goitre. FNACC does not allow for the

establishment of a clear diagnosis in 15–30% of cases (mainly follicular lesions). Molecular biology techniques can be useful, allowing for the detection, in FNACC smears, of the known mutations involved in the oncogenesis.
Aim
To evaluate the usefulness of the detection of the BRAF mutation in FNAC in the early diagnosis of TC.
Material and methods
The study involved 1590 consecutive patients examined for 2 years and 2290 FNACC were performed. The FNAC results were classified according to the Bethesda system. In the case of the cytological results group 3,4,5 the molecular analysis was performed in order to detect BRAF mutation using the combination of Sanger sequencing, ASA-PCR and qPCR techniques. All the patients with BRAF mutation were operated on.
Results
Out of 2290 FNACC in groups 3,4,5 there were classified 106,29,12 respectively. Molecular analysis showed the presence of the BRAF mutation in a total of 12 cases (8.2%): three positive cytopathological results out of 106- in group 3; 0 out of 29 in group 4, and 9 positive out of 12- in group 5. Histopathological studies confirmed the presence of PTC in all the 12 patients with BRAF mutation present.
Conclusions
The presence of BRAF mutation in FNACC material is always associated with the presence of PTC, however from the clinical point of view the confirmation of the presence of mutations is of little help in early diagnosis. Revealing the BRAF mutation has resulted in a change of procedure only in the case of three patients, with cytological group 3, in the remaining nine cases from group 5 – the cytology procedure was enough to indicate those patients eligible for surgery.

DOI: 10.1530/endoabs.37.OC6.4

OC6.5

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

Eliska Vaclavikova[1], Sarka Dvorakova[1], Vlasta Sykorova[1], Josef Vcelak[1], Tereza Halkova[1], Petr Vlcek[2] & Bela Bendlova[1]
[1]Institute of Endocrinology, Dept. of Molecular Endocrinology, Prague, Czech Republic; [2]2nd Faculty of Medicine in Charles University and University Hospital Motol, Dept. of Nuclear Medicine and Endocrinology, Prague, Czech Republic.

Introduction
Hereditary medullary thyroid carcinoma (MTC) is associated with only one major cause – germline mutations in the *RET* proto-oncogene. The most of tested families with MTC is related to specific *RET* mutation, however, very small number of families left unresolved without the causing inherited mutation. New techniques of next generation sequencing give hope in finding the new candidate genes that could be involved in the pathogenesis of these MTC families.
Methods
We performed *RET* genetic screening in 870 individuals – 490 patients and 380 at-risk-relatives. The germline *RET* mutation was detected in 58 families (83% of familial and 7% of apparently sporadic MTCs). No mutation in all *RET* exons was found in six families with clinically supposed hereditary form of MTC (4 FMTC and 2 MEN2A phenotype). Six index patients of these families were analyzed using Trusight Cancer Sequencing Panel (Illumina) that targeted 94 genes associated with cancer. After exclusion of common single nucleotide polymorphisms, the data were focused on novel or rare non-synonymous variants in coding sequences and tested *in silico* (SIFT, PolyPhen) for possible damaging effect.
Results
Several promising variants in each patient have been identified in genes involved in key processes for cancer development such as repair genes. Considering SIFT and PolyPhen evaluation, the analysis has discovered very rare variants in genes *RHBDF2*, *XPA*, *MET* and *CHEK2*. The variants detected in *APC* and *EZH2* were previously investigated in association with other cancers. Three patients have a pathogenic polymorphism in *HNF1A*.
Conclusion
New candidate genes can represent genetic modifying factors or crucial genes in each family. Although detected alterations are promising, it is necessary to verify them in other affected family members.
Disclosure
This work was supported by the grant projects IGA MH CZ NT13901-4 and MH CZ DRO 00023761.

DOI: 10.1530/endoabs.37.OC6.5

Neuroendocrinology and pituitary-basic

OC7.1

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

Joyce Schuilwerve[1], Melitza Elizabeth[1], Robin Peeters[1], Theo Visser[1], Anita Hokken-Koelega[2,3] & Laura de Graaff[1,3]
[1]Erasmus Medical Center, Rotterdam, The Netherlands; [2]Erasmus MC Sophia, Rotterdam, The Netherlands; [3]Growth Research Foundation, Rotterdam, The Netherlands.

Introduction
POU1F1 is a pituitary transcription factor, critical for differentiation of pituitary somatotrophs, thyrotrophs and lactotrophs. *POU1F1* expression depends on the presence of PROP1, which attenuates expression of transcriptional repressor *HESX1*. Previous mutation screening of *POU1F1* coding exons in our cohort of patients with combined pituitary hormone deficiency (CPHD) showed *POU1F1* mutations in only 1% of the families. We hypothesised that defects in the regulatory region of *POU1F1* might explain the phenotype of CPHD.
Patients and methods
We screened the regulatory regions of *POU1F1*, as well as those of *PROP1* and *HESX1* among 87 patients with CPHD (62M/25F). Since patients with *HESX1* mutations can initially present with IGHD only, we also screened 92 patients with IGHD (64M/28F). We compared genotype frequencies in our CPHD cohort with those found in controls from the 1000 genomes project and we studied *PROP1* and *POU1F1* promoter SNPs in relation to phenotypic data.
Results
We found a new variant in the *POU1F1* promoter. We are currently performing promoter-luciferase reporter assays, since *in silico* analysis of the new variant showed potential effects on promoter activity by creating a new binding site for several transcription factors. In addition, we found two known SNPs in the *POU1F1* promoter and six known SNPs in the *PROP1* promoter. We did not find any variant in the *HESX1* promoter. Rs148607624, a three nucleotide deletion in the *PROP1* promoter which has previously been associated with CPHD, showed a relation with IGF1 levels in our CPHD patients.
Conclusion
We screened the regulating regions of pituitary transcription factors *POU1F1, PROP1* and *HESX1* in our cohort of CPHD patients and found a new variant in the *POU1F1* promoter region. We will present detailed phenotypic data of the patient carrying the new variant. We will show the impact of the new variant on *POU1F1* promoter activity.

DOI: 10.1530/endoabs.37.OC7.1

OC7.2

KLF4 in hypothalamus regulates leptin homeostatic effects through AgRP

Estrella Sanchez-Rebordelo[1], Monica Imbernon[1,3], Rosalia Gallego[2], Marina Gandara[2], Pamela Lear[1], Miguel Lopez[1,3], Carlos Dieguez[1,3] & Ruben Nogueiras[1,3]
[1]Department of Physiology of Santiago de Compostela, Instituto de Investigación Sanitaria, Santiago de Compostela, Spain; [2]Department of Morphological Sciences, School of Medicine, Insitituto de Investigación Sanitaria, University of Santiago de Compostela, Santiago de Compostela, Spain; [3]CIBER Fisiopatología de la Ovesidad y Nutrición (CIBERobn), Santiago de Compostela, Spain.

Introduction
Krüpel-like factor 4 (KLF4) is a zinc-finger-type transcription factor expressed in a range of tissues that plays multiple functions. KLF4 is expressed in neural stem cells and is critical to neuronal differentiation. Recent evidence suggests that KLF4 also plays an important role in the central regulation of energy balance. *In vitro* studies show that KLF4 is a transcriptional regulator of agouti–related protein (AgRP), essential to the hyperphagic response.
Description of methods/design
Sprague Dawley rats, WT and ob/ob mice. Stereotaxic microinjection of adenoviral and lentiviral expression vectors. Body composition, locomotor activity and indirect calorimetry. Leptin central pathway studies. Leptin sensitivity assays. Immunohistochemistry. Western blotting. Liver trygliceride content.
Results
We report that hypothalamic KLF4 represents a new transcription factor specifically modulating agouti-related protein (AgRP) expression *in vivo*.

Hypothalamic KLF4 colocalises with AgRP neurons and is modulated by nutritional status and leptin. Over-expression of KLF4 in the hypothalamic arcuato nucleus (ARC) induces food intake and increases body weight through the specific stimulation of AgRP, as well as blunting leptin sensitivity in lean rats independent of forkhead box protein 01 (FoxO1). Down-regulation of KLF4 in the ARC inhibits fasting-induced food intake in both lean and diet-induced obese (DIO) rats. Silencing KLF4, however, does not, on its own, enhance peripheral leptin sensitivity in DIO rats.

Conclusion

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

Disclosure

Ministerio de Economía y Competitividad (CD: BFU2011-29102; RN: RYC-2008-02219 and BFU2012-35255), Xunta de Galicia (ML: 10PXIB208164PR and 2012-CP070; RN: EM 2012/039 and 2012-CP069). European Community's Seventh Framework Programme: CD, ML and RN.

DOI: 10.1530/endoabs.37.OC7.2

OC7.3

Maternal distress associates with placental genes regulating foetal glucocorticoid exposure and IGF2: role of obesity and sex

Theresia Mina[1,4], Katri Räikkönen[2], Simon Riley[3,4], Jane Norman[3,4] & Rebecca Reynolds[1,4]

[1]Queen's Medical Research Institute, BHF Centre for Cardiovascular Sciences, University of Edinburgh, Edinburgh, UK; [2]Institute of Behavioral Sciences, University of Helsinki, Helsinki, Finland; [3]Queen's Medical Research Institute, MRC Centre for Reproductive Health, University of Edinburgh, Edinburgh, UK; [4]Queen's Medical Research Institute, Tommy's Centre for Maternal and Fetal Health, University of Edinburgh, Edinburgh, UK.

Introduction

Maternal distress, including poorer life satisfaction, increased anxiety and depression (A&D) symptoms, are worse in Severely Obese (SO) than lean pregnancy and may alter placental genes regulating foetal glucocorticoid exposure and placental growth. We hypothesised that the associations between increased maternal distress with changes in placental mRNA levels leading to a reduced placental barrier to maternal glucocorticoids, and altered placental IGF2, are more pronounced in SO pregnancy. We also considered any sex-specific effects.

Methods

Placental mRNA levels of genes regulating glucocorticoids including 11β-HSDs, NR3C1, NR3C2, ABC transporters, mTOR and IGF2 family were measured in term placental samples from 43 lean (BMI $\leq 25\ kg/m^2$) and 50 SO (BMI $\geqq 40\ kg/m^2$) women, in whom A&D symptoms were prospectively evaluated during pregnancy.

Results

The mRNA levels of genes with a similar role in regulating foetal glucocorticoid exposure were strongly inter-correlated (all $0.2 \leq \leq 0.7$, $P \leq 0.05$). Increased A&D symptoms associated with increased NR3C2 and IGF2 in both lean and SO group (all ≤ 0.3, $P \leq 0.05$). Increased maternal distress was associated with higher ABCB1 and ABCG2 mRNA levels in SO but lower ABCB1 and higher 11β-HSD1 mRNA levels in lean (all $P \leq 0.05$) suggesting a protective adaptive response in SO placentas. Increased maternal distress associated with reduced mRNA levels of ABCB1, ABCG2, 11β-HSD2, NR3C1and IGF2 in female placentas (all ≤ 0.29, $P \leq 0.05$), but not in males.

Conclusion

The observed sex differences in placental responses suggest greater vulnerability of female foetuses to maternal mood with potentially greater fetal glucocorticoid exposure and excess IGF2. Further studies are needed to test whether this translates to potentially greater negative outcomes of maternal distress in females in early childhood.

Disclosure

We are grateful to the generous funding from Tommy's the Baby Charity and Principal Development Scholarship, Charles Darwin Scholarship and Global Research Scholarship, University of Edinburgh, Scotland.

DOI: 10.1530/endoabs.37.OC7.3

OC7.4

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

Silvia Leon[1,2], Maria Jesus Vazquez[1,3], Alexia Barroso[1,2], David Garcia-Galiano[1], Francisco Ruiz-Pino[1,2], Maria Manfredi-Lozano[1,2], Antonio Romero-Ruiz[1,2], Miguel A Sanchez-Garrido[1,3], Carlos Dieguez[3,4], Ruben Nogueiras[3,4], Juan Roa[1,2], Leonor Pinilla[1,2] & Manuel Tena-Sempere[1,2]

[1]University of Cordoba, Cordoba, Spain; [2]Instituto Maimonides de Investigacion Biomedica de Cordoba (IMIBIC), Cordoba, Spain; [3]CIBERobn, Cordoba, Spain; [4]University of Santiago de Compostela, Santiago de Compostela, Spain.

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

Disclosure

This work was supported by grant BFU2011-025021 (Ministerio de Economía y Competitividad, Spain; co-funded with EU funds from FEDER Program) and Projects P08-CVI-03788 and P12-FQM-01943 (Junta de Andalucía, Spain).

DOI: 10.1530/endoabs.37.OC7.4

OC7.5

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

Raúl M Luque[1], Manuel D Gahete[1], Sergio Pedraza-Arévalo[1], Ana I Pozo-Salas[1], Fernando L-López[1], Luis de Lecea[3], José Córdoba-Chacón[1,2] & Justo P Castaño[1]

[1]Department of Cell Biology, Physiology and Immunology, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Hospital Universitario Reina Sofía, University of Córdoba, Campus de Excelen, Córdoba, Spain; [2]Research and Development Division, Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, Jesse Brown Veteran Affairs Medical Center, University of Illinois at Chicago, Chicago, Illinois, USA; [3]Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California, USA.

Somatostatin (SST) and cortistatin (CORT) are two highly related neuropeptides involved in the regulation of several endocrine secretions. In particular, SST and CORT are two primary negative regulators of GH secretion. Consequently, SST or CORT knockout (KO) mice exhibit elevated GH levels; however, this does not lead to increased IGF-I levels or somatic growth, which has been suggested that

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

Funding
This work was supported by Junta de Andalucía (CTS-1406, BIO-0139, PI-0639-2012) Ministerio de Economía y Competitividad, Gobierno de España (BFU2013-43282-R), Instituto de Salud Carlos III (PI13/00651), Centro de Investigación Biomédica en Red de la Fisiopatología de la Obesidad y Nutrición (CIBERobn) and Ayuda Merck Serono 2013.

DOI: 10.1530/endoabs.37.OC7.5

Endocrine tumours

OC8.1

A role for vault particles as a marker for therapeutic effects against endocrine tumours

Constanze Hantel & Felix Beuschlein
Endocrine Research Unit, Medizinische Klinik and Poliklinik IV, Ludwig-Maximilians-University, Munich, Germany.

The vault complex, consisting of a major vault protein (MVP), two minor vault proteins (VPARP and TEP1) and small untranslated RNA molecules (vault RNAs 1–4), is considered the largest intracellular ribonucleoprotein particle. Although in recent years, vaults were believed to be involved in multidrug resistance, the exact function of this complex has remained unclear. Recently, we investigated the therapeutic applicability of a Tumour-Vascular-Disrupting Agent (ASA) in preclinical models for neuroendocrine tumours of the gastroenteropancreatic system (BON) and adrenocortical carcinoma (NCIh295R). Upon treatment we detected highly significant anti-tumoural effects in BON xenografts which were not evident in NCI-H295R. In an attempt to explain differences in therapeutic responsiveness, gene expression patterns within these tumours were investigated by a gene array. Subsequent analyses identified vault RNAs 1–3 as the most pronounced regulated transcripts in the tumour model showing therapeutic responsiveness. Quantitative real time PCR confirmed these results for ASA treated BON tumours (% of 100% controls; vault1: $2468.1 \pm 367\%$, $P<0.001$; vault2: $1922.5 \pm 235\%$, $P<0.001$; vault3: $901.3 \pm 119\%$, $P<0.001$) while no changes were detectable for the not-responding NCI-H295R-xenografts (% of 100% controls; vault1: $224.1 \pm 84\%$, $P>0.05$; vault2: $113 \pm 23\%$, $P>0.05$; vault3: $89 \pm 14\%$, $P>0.05$). Subsequently, we investigated NCI-H295R-xenografts which had been treated with two different chemotherapeutic regimens (EDP-M and LEDP-M). In this therapeutic setting treatment-dependent upregulation of vault RNAs could also be detected in NCI-H295R-tumors (% of 100% controls; vault1: EDP-M $296.3 \pm 44\%$, $P<0.001$; LEDP-M $243.5 \pm 16\%$, $P<0.001$; vault2: EDP-M $157.2 \pm 20\%$, $P>0.05$; LEDP-M $160.7 \pm 20\%$, $P>0.05$; vault3: EDP-M $241.2 \pm 55\%$, $P<0.001$; LEDP-M $118.9 \pm 16\%$, $P>0.05$). Further *in vitro* analyses revealed dynamic changes in vault RNA expression also upon blasticidin, doxorubicin, mitotane treatment and a significant increase in MVP protein levels upon TNF alpha treatment in BON cells. In summary, further investigation and modulation of vault particles might have potential to improve efficacy of anticancer drugs in endocrine tumours.

Disclosure
This work was supported by the Wilhelm-Sander-Stiftung (grant number 2011.103.1).

DOI: 10.1530/endoabs.37.OC8.1

OC8.2

Role of microenvironment on neuroblastoma SK-N-AS SDHB silenced cell metabolism and function

Elena Rapizzi[1], Rossella Fucci[1], Elisa Giannoni[2], Letizia Canu[1], Susan Richter[3], Paolo Cirri[2] & Massimo Mannelli[1,4]
[1]Endocrinology Unit, Department Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy; [2]Biochemistry Unit, Department Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy; [3]Institute of Clinical Chemistry and Laboratory Medicine, Technische Universität Dresden, University Hospital Carl Gustav Carus, Dresden, Germany; [4]Istituto Toscano Tumori, Florence, Italy.

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

Disclosure
Fondazione Cassa di Risparmio di Pistoia e Pescia (Prot. 2013.0375).
Ente Cassa di Risparmio di Firenze research fellowship (Prot.2013.0503).

DOI: 10.1530/endoabs.37.OC8.2

OC8.3

miR-372 is aberrantly expressed in most parathyroid tumours and might contribute to parathyroid tumourigenesis by inhibiting CDKN1A/p21 and LATS2

Chiara Verdelli[1], Irene Forno[2], Valentina Vaira[2,3], Vito Guarnieri[4], Alfredo Scillitani[5], Filomena Cetani[6], Leonardo Vicentini[7], Gianni Balza[8], Edoardo Beretta[9] & Sabrina Corbetta[10]
[1]Laboratory of Molecular Biology, IRCCS Policlinico San Donato, San Donato Milanese, MI, Italy; [2]Division of Pathology, IRCCS Fondazione Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; [3]Istituto Nazionale Genetica Molecolare (INGM) Romeo ed Enrica Invernizzi, Milan, Italy; [4]Medical Genetics, IRCCS Hospital Casa Sollievo della Sofferenza, San Giovanni Rotondo, FG, Italy; [5]Endocrinology Unit, IRCCS Hospital Casa Sollievo della Sofferenza, San Giovanni Rotondo, FG, Italy; [6]Endocrine Unit 2, Department of Clinical and Experimental Medicine, University Hospital of Pisa, University of Pisa, Pisa, Italy; [7]Endocrine Surgery, IRCCS Fondazione Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; [8]General Medicine Unit, AO Alessandro Manzoni, Lecco, Italy; [9]Endocrine Surgery, IRCCS Ospedale San Raffaele, Milan, Italy; [10]Endocrinology and Diabetology Unit, Department of Biomedical Sciences fro Health, University of Milan, IRCCS Policlinico San Donato, San Donato Milanese, MI, Italy.

We previously described aberrant expression of microRNAs belonging to the chromosome 19 cluster (C19MC) and the close miR-371-373 cluster in two-thirds of parathyroid carcinomas (PCas). Therefore, we investigated the involvement of the miR-371-373 cluster in parathyroid tumours, where miR-372 was the most consistently upregulated. miR-372 is known to be highly expressed in human

embryonic stem cells and definitely downregulated upon differentiation. Moreover, miR-372 promotes human somatic cell reprogramming. miR-372 was expressed at high levels (more than fourfold) in 48 out of 79 parathyroid tumours compared with the expression levels in normal parathyroid glands ($n=5$). miR-372 was expressed in more than 75% of both atypical parathyroid adenomas (PAds; $n=18$; 5.9 ± 0.8-fold, $P=0.003$) and PCas ($n=15$; 5.1 ± 1.1-fold, $P=0.01$) at levels significantly higher than those in typical PAds ($n=46$; 2.1 ± 0.7-fold). miR-372 overexpression in HEK293 and MCF7 cells significantly downregulated mRNA and protein levels of the cyclin inhibitor kinase CDKN1A/p21 and of the large tumour suppressor kinase 2 (LATS2). Similarly, *CDKN1A* and *LATS2* mRNA levels were significantly downregulated by the miR-372 overexpression in typical PAds-derived cells. miR-372 overexpression attenuated the Go/G1 checkpoint in the cell cycle, reducing the proportion of cells in the Go/G1 phase from 70 to 59%. Furthermore, miR-372 has been related with the 'stemness' Wnt/β-catenin signalling pathways. In 16 typical PAds we found that miR-372 levels were positively correlated with the nuclear β-catenin accumulation, investigated by western blot, and with the mRNA levels of the direct gene target of nuclear β-catenin transcriptional activity *AXIN2*. Nonetheless, in typical PAds-derived cells ($n=6$) miR-372 expression levels were not affected by lithium chloride-induced nuclear β-catenin accumulation. In conclusion, i) miR372 was aberrantly expressed in a subset of parathyroid tumours; ii) atypical PAds and PCas expressed miR-372 more frequently and at higher levels than typical PAds; iii) *CDKN1A/p21* and *LATS2* were targets of miR-372 inhibitory effects in PAds-derived cells; iv) miR-372 aberrant expression might impair Wnt/β-catenin pathway in parathyroid tumour cells.

Disclosure
This work was supported by the IRCCS Policlinico San Donato Research Found.
DOI: 10.1530/endoabs.37.OC8.3

OC8.4

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

Dalia Somjen[1], Sara Katzburg[1], Batya Gayer[2], Roni Kasher[3], Forune Kohen[2], Orli Sharon[1] & Naftali Stern[1]
[1]Institute of Endocrinology, Tel-Aviv Medical Center and the Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv 64239, Israel; [2]Department of Biological Regulation, The Weizmann Institute of Science, Rehovot 76100, Israel; [3]Department of Desalination and Water Treatment, Zuckerberg Institute for Water Research, The Blaustein Institutes for Desert Research, Ben-Gurion University of the Negev, Sede-Boqer Campus 84990, Israel.

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

DOI: 10.1530/endoabs.37.OC8.4

OC8.5

Oestrogen receptor α promotes prostate cancer progression through dual actions in both epithelia and stroma

Mitchell Lawrence[1], Ruth Pidsley[2], Stuart Ellem[1], Luc Furic[1], Shalima Nair[2], Hugh French[2], Aaron Stratham[2], Ola Larsson[3], Mark Frydenberg[1], John Pedersen[5], Grant Buchanan[4], Renea Taylor[1], Susan Clark[2] & Gail Risbridger[1]
[1]Monash University, Melbourne, Victoria, Australia; [2]Garvan Insitute of Medical Research, Sydney, New South Wales, Australia; [3]Karolinska institutet, Stockholm, Sweden; [4]University of Adelaide, Adelaide, South Australia, Australia; [5]Tissupath Pathology Services, Melbourne, Victoria, Australia.

In human prostate, Oestrogen receptor α (ERα) expression in the epithelium increases with tumour Grade and promotes proliferation involving classical genomic and rapid non-genomic signalling, as well as transcription regulation of non-coding RNA. Similarly, in the tumour stroma there is up-regulation of ERα, corresponding with declining AR, resulting in a higher ratio of ERα:AR with increasing Grade. Additionally, in prostate cancer-associated fibroblasts (CAFs) we reported an oestrogen-regulated gene expression signature and showed CXCL12 (SDF-1) was the most highly over-expressed gene. Functional assays showed that the CXCL12 secreted by CAFs recruits mast cells via CXCR4, with mast cells in turn expressing ERα, activated by oestrogen, and exhibiting altered pro-inflammatory chemokine/cytokine expression in response to oestrogen. To identify the mechanism regulating oestrogen gene expression in stroma, we examined patient-matched CAFs and normal prostate fibroblasts (NPFs) from prostatectomy specimens from a cohort of ten patients. We observed hypomethylation of the promoter of ESR1 gene (encoding ERα), which correlated with a higher ERα mRNA abundance in CAFs vs NPFs. To investigate if there was evidence of a broader role of epigenetic gene regulation, we used whole genome bisulphite sequencing to compile the first complete epigenome map of the human prostate tumour stroma. In addition to ESR1, there were >300 differentially methylated regions, including global hypomethylation and focal hypermethylation, in CAFs vs NPFs. Collectively, these data demonstrate that epigenomic changes in tumour stroma are a mechanism underlying the enduring functional differences between NPFs and CAFs. This includes epigenetically-regulated genes, such as ESR1, that are implicated in prostate cancer progression. These results warrant similar studies to determine if ERα is epigenetically regulated in epithelia, especially in advanced prostate cancer.

Disclosure
National Health & Medical Research Council, ID: 1002648, 1020959, 1035721 & 1003247.
Prostate Cancer Foundation of Australia (Movember), ID: YI0911.
Cancer Australia, ID: 1044458CA.
DOI: 10.1530/endoabs.37.OC8.5

Adrenal 2

OC9.1

Effects of dexamethasone and adrenocorticotropin on circulating microRNA expression in humans

Ivan Igaz[1], Gabor Nyiro[2], Zoltan Nagy[3], Pal Perge[3], Miklos Toth[3], Karoly Racz[2,3], Peter Igaz[3] & Attila Patocs[4]
[1]Szent Imre Teaching Hospital, Budapest, Hungary; [2]Molecular Medicine Research Group, Hungarian Academy of Sciences and Semmelweis University, Budapest, Hungary; [3]Semmelweis University, Budapest, Hungary; [4]'Lendulet-2013' Hereditary Endocrine Tumors Research Group, Budapest, Hungary.

Objective
MicroRNAs are short non-protein coding RNA molecules involved in the regulation of numerous homeostatic processes via modulating gene expression. There are some data that the expression of microRNA might be modulated by hormones, but the interaction of hormones and circulating microRNAs of adrenocortical origin is mostly unknown.
Methods
The expression of six selected circulating microRNAs (hsa-miR-27a, hsa-miR-125b-2, hsa-miR-200b, hsa-miR-214, hsa-miR-483-5p, hsa-miR-503) was studied in plasma samples of ten individuals examined by 1 mg dexamethasone suppression test and another ten individuals stimulated by 250 μg tetracosactide (adrenocorticotropin). Total RNA was isolated from plasma samples and microRNA expression has been analysed by Taqman RT-qPCR normalized to cel-miR-39 as reference. The expression of hsa-miR-27a was also studied *in vitro* in NCI-H295R adrenocortical cell line.
Results
From the six circulating microRNAs selected for the *in vivo* study based on literature data showing their association to adrenocortical cancer or their responsiveness to hormonal stimuli in animal models, only circulating hsa-miR-27a proved to be significantly modulated *in vivo*: its expression was up-regulated by dexamethasone whereas it was suppressed by adrenocorticotropin. Expression of secreted *hsa-miR-27a* was significantly induced in culture supernatants of NCI-H295R cells, as well.
Conclusions
hsa-miR-27a expression is modulated by hormones of the hypothalamic-pituitary-adrenal axis both *in vitro* and *in vivo*. Dexamethasone induced secreted hsa-miR-27a both *in vitro* and circulating hsa-miR-27a *in vivo*. The expression of circulating hsa-miR-483-5p proposed as diagnostic marker for adrenocortical malignancy was not affected by dexamethasone or tetracosactide administration supporting its usefulness for the evaluation of malignancy of adrenocortical lesions.
Disclosure
Hungarian Scientific Research Grant (OTKA K100295 to Peter Igaz; OTKA PD100648 to Attila Patocs) and Technology Innovation Fund, National Developmental Agency (KTIA-AIK-2012-12-1-0010).

DOI: 10.1530/endoabs.37.OC9.1

OC9.2

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

Christopher Jones[1], Ashwini Mallappa[2], Nicole Reisch[3], Beverley Hughes[1], Donna O'Neil[1], Nils Krone[1], Martin Whitaker[4], David Eckland[4], Deborah Merke[2], Richard Ross[4,5] & Wiebke Arlt[1]
[1]Centre for Endocrinology, Diabetes and Metabolism, University of Birmingham, Birmingham, UK; [2]National Institute of Health Clinical Center, Bethesda, Maryland, USA; [3]Medizinische Klinik und Poliklinik IV, Ludwig-Maximilians-Universität München, Munich, Germany; [4]Academic Unit of Endocrinology, Department of Human Metabolism, University of Sheffield, Sheffield, UK; [5]Diurnal Ltd, Cardiff, UK.

Suppression of excess androgen production poses a considerable clinical challenge in the management of patients with congenital adrenal hyperplasia (CAH). Whilst the major route of androgen synthesis in humans is the classic pathway via androstenedione and testosterone, the relative contribution of the alternative pathway originating from 17-hydroxyprogesterone to androgen excess in CAH has not been defined. Androgen effects of both pathways are elicited in androgen target tissues by the action of the most potent androgen receptor agonist, 5alpha-dihydrotestosterone (DHT). Here we carried out urinary steroid metabolome profiling by gas chromatography/mass spectrometry in conjunction with serum steroid analysis and clinical phenotyping in patients with CAH due to 21-hydroxylase deficiency. Our aim was to determine the extent to which the alternative androgen synthesis pathway contributes to DHT production in CAH and to examine the potentially differential impact of conventional and modified delayed glucocorticoid therapy.
In a cross-sectional study we analysed 24 h-urinary steroid excretion in 40 patients with CAH on conventional glucocorticoid replacement with hydrocortisone ($n=12$), prednisolone ($n=23$) and dexamethasone ($n=5$) in comparison to 80 sex- and age-matched healthy controls. CAH patients had significantly higher excretion of 5alpha-17HP, the signature metabolite of the alternative pathway, representing 0.97% of the 5alpha-reduced androgen pool in healthy controls, but 15.12% in patients with CAH. In an interventional study we treated 16 adults with classic CAH (eight females; age 29 ± 13 years; 12 salt-wasting, four simple virilising) with Chronocort, a modified and delayed release hydrocortisone preparation that mimics the physiological diurnal secretion profile of cortisol. Twenty-four hour urinary steroid excretion was analysed at baseline on conventional glucocorticoid therapy and after six months of Chronocort. Results revealed that Chronocort significantly reduced both the absolute amount and the relative percentage of 5a17HP (conventional HC 21.5% vs Chronocort 12.3%), concurrently exerting improved biochemical control with regard to overall and 5alpha-reduced androgen output.
Disclosure
This research was supported in part by the Intramural Research Program of the NIH and in part by Diurnal Ltd UK.

DOI: 10.1530/endoabs.37.OC9.2

OC9.3

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

Miguel Debono[1], Robert Harrison[1], Brian Keevil[2], Martin Whitaker[3], Dena Digweed[3], Wiebke Arlt[3,4] & Richard Ross[1,3]
[1]University of Sheffield, Sheffield, UK; [2]University of Manchester, Manchester, UK; [3]Diurnal Limited, Cardiff, UK; [4]University of Birmingham, Birmingham, UK.

Introduction
Measuring serum cortisol to evaluate the normal circadian rhythm and adequacy of hydrocortisone replacement levels requires multiple readings; an expensive, cumbersome process. Conversely, salivary cortisone, a surrogate marker for free cortisol levels is non-invasive and well suited for out-patient settings. We hypothesised that salivary cortisone predicts circulating cortisol levels and can be used as an alternative marker of serum cortisol in a physiological setting or in patients on hydrocortisone replacement.
Methods
This was an observational study in 14 healthy male volunteers who had hourly serum cortisol measurements over 24 h in addition to salivary cortisol and cortisone measurements from 1500 h to 2200 h and from 0700 h to 1500 h; all measurements were carried out by liquid chromatography/tandem mass spectrometry. Relationships between serum and salivary cortisol/cortisone were assessed by individual correlation analysis and linear mixed effects modelling. A similar analysis was carried out after 20mg of oral and i.v. hydrocortisone given on different days after dexamethasone suppression.
Results
Correlation analysis (ρ), for the relationship between endogenous log-transformed salivary cortisone or salivary cortisol with serum cortisol rhythm, ranged from 0.96 to 0.99; $P<0.001$ and from 0.84 to 0.99; $P<0.001$, respectively. Salivary cortisone was superior to salivary cortisol (range R^2: 0.93–0.99 vs 0.71–0.97) in predicting circulating, serum cortisol. By fitting a mixed effects model to predict serum cortisol levels from salivary cortisone (predicted serum cortisol (nmol/l) = (13.57 + individual-specific random effects) × salivary cortisone (nmol/l)) correlation ρ and R^2 between measured and predicted serum cortisol were 0.91 and 0.82 under physiological conditions, 0.89 and 0.66 for 20 mg oral hydrocortisone and 0.93 and 0.72 for 20 mg i.v. hydrocortisone, respectively.
Conclusion
Salivary cortisone levels are strongly related to serum cortisol and repetitive measurements of salivary cortisone may be used to predict the serum cortisol rhythm and cortisol levels after hydrocortisone.
Disclosure
This work was supported by the European Commission (HEALTH-FP7; Project No: 281654).

DOI: 10.1530/endoabs.37.OC9.3

OC9.4

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

Gesine Meyer[1], Klaus Badenhoop[1] & Roland Linder[2]
[1]Division of Endocrinology, Department of Medicine 1, Goethe-University-Hospital Frankfurt, Frankfurt, Germany; [2]WINEG, Scientific Institute of the TK for Benefit and Efficiency in Health Care, Hamburg, Germany.

Introduction
Adrenal crises are potentially life-threatening complications in patients with adrenal insufficiency (AI). Our objective was to investigate the frequency of adrenal crises in patients with different forms of AI in the Techniker Krankenkasse (TK), one of the largest German Health Insurance providers, covering more than 12% of the German population.
Design
The Statutory Health Insurance (SHI) database of the TK was analysed for diagnostic codes over an observation period from 01.01.2010 to 31.12.2013. Adjusting data for age and sex, $n=11691$ diagnoses of AI were recorded and classified in primary ($n=4231$), respectively secondary ($n=7460$) AI. Additionally, the subgroup with autoimmune polyglandular syndrome (APS) comprising AI was defined ($n=1487$). A query for ICD-code E27.2 (adrenal crisis) was performed in these cohorts.
Results
In our cohort, we found a prevalence of 222/million for secondary and 126/million for primary AI. Adrenal crises were documented with a frequency of 4.8/100 patient years. Crises were significantly more frequent in patients with primary (7.6/100 patient years) compared to those with secondary AI (3.2/100 patient years; $P<0.0001$). Prevalence of crises was higher in individuals with APS comprising primary AI (10.9/100 patient years) and highest in patients with primary AI and type 1 diabetes (12.5/100 patient years).
Conclusions
Applying the SHI database of the TK, comprising more than 8 million individuals, we identified profound data about the risk of adrenal crises in different groups of patients with AI. For the first time our data confirm and extend the clinical observation, that patients with primary AI and additional autoimmune endocrinopathies are at highest risk for adrenal crises. Approximately one of eight patients with primary AI and type 1 diabetes suffers from an adrenal crisis per year. These data provide a basis for specific targeting of efforts aiming at the prevention of adrenal crises.
Disclosure
This work was supported by the European Union 7th framework Health programm FP7 with the acronym EURADRENAL under the grand agreement 2008-201167.

DOI: 10.1530/endoabs.37.OC9.4

OC9.5

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

Cristina Ronchi[1], Silviu Sbiera[1], Barbara Altieri[1], Sonja Steinhauer[1], Vanessa Wild[2], Michaela Bekteshi[1], Matthias Kroiss[1], Martin Fassnacht[1] & Bruno Allolio[1]
[1]Endocrine and Diabetes Unit, University Hospital Wuerzburg, Wuerzburg, Germany; [2]Institute of Pathology, University of Wuerzburg, Wuerzburg, Germany.

Background
Adrenocortical tumours consist of frequent adrenocortical adenomas (ACA) and highly malignant (ACC) with a still incompletely understood pathogenesis. Dysregulation of Notch signalling pathway is implicated in several cancers with oncogenic or tumour suppressor functions. Copy number gains and over-expression of Jagged1**,** a ligand of Notch receptor, was reported in ACC. The aim of the study was to evaluate the expression of Jagged1 and other Notch-related factors in adrenocortical tumors and to correlate it with clinical outcome.
Material and methods
mRNA expression of JAG1, NOTCH1, CTNNB1, and selected target genes of Notch signalling (HES1, HES5 and HEY2) and Wnt/β-catenin pathway (LEF1) was evaluated in 80 fresh frozen samples (28 normal adrenal glands=NAG, 24 ACA, 28 ACC) by quantitative real-time PCR. Immunohistochemistry was performed in 221 tissues on paraffin slides (16 NAG, 27 ACA, 178 ACC) for Jagged1, activated Notch1 (aNotch1) and HEY2 staining. The relationship with nuclear β-catenin expression was also investigated.
Results
mRNA expression of JAG1, NOTCH1, CTNNB1, and target genes was not significantly different between normal and neoplastic adrenal glands. At protein level, all factors evaluated were highly expressed (*H*-score 2–3) in a larger proportion of ACCs than in ACAs and NAG (Jagged1 in 27, 15 and 10% of NA, respectively, $P=0.0004$; aNotch1 in 13%, 8% and none of NAG, $P<0.0001$; HEY2 in 66, 61 and 33%, $P=0.0001$). High Jagged1 expression was associated with earlier ENSAT tumour stages ($P=0.07$) and lower number of metastases ($P=0.08$) in ACC. Accordingly, high Jagged1 levels impacted favourably on overall survival ($n=168$, 131 vs 30 months, $P=0.0023$, HR=0.45) and progression free survival (37 vs 9 months, $P=0.0023$, HR=0.51), even after adjustment for ENSAT tumour stage ($P=0.005$) and nuclear β-catenin expression ($P=0.009$).
Conclusion
Jagged1 is overexpressed in a subgroup of ACCs, being associated with a more differentiated phenotype and better clinical outcome. Notch1 signaling pathway activation might be involved in adrenocortical tumor progression, but still needs to be better investigated.
Disclosure
This work was supported by the Wilhelm Sander Foundation (grant number 2012.095.1).

DOI: 10.1530/endoabs.37.OC9.5

Nuclear receptors and signalling

OC10.1

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

Yacir Benomar[1,2], Arieh Gertler[3] & Mohammed Taouis[1,2]
[1]Molecular Neuroendocrinology of Food Intake, UMR9197, University Paris Sud, Orsay, France; [2]Molecular Neuroendocrinology of Food Intake, Neuroscience Paris-Saclay Institute, CNRS UMR 9197, University Paris Sud, Orsay, France; [3]Faculty of Agricultural, Food and Environmental Quality Sciences, The Institute of Biochemistry, Food Science, and Nutrition, The Hebrew University of Jerusalem, Rehovot, Israel.

Obesity is linked to common metabolic diseases including insulin resistance, which constitutes a principal risk factor for type 2 diabetes. Increasing evidence indicates that changes in adipose-secreted factors in obesity, dramatically affect insulin sensitivity. Among these adipokines, resistin is described as a key factor in obesity-mediated both inflammation and insulin resistance. However, little is known about the molecular mechanisms mediating resistin effects particularly at the neuronal level. Recently, we have shown that central resistin acts by way of hypothalamic TLR4 receptors promoting overall inflammation and insulin resistance. Adiponectin is another adipokine with anti-diabetic and insulin sensitizing properties. A decrease in adiponectin level and action has been linked to insulin resistance. Here, we aim to investigate whether resistin could contribute to insulin resistance trough the impairment of adiponectin action. To test this hypothesis we examined the impact of resistin overexposure on adiponectin signaling in human neuronal cells SH-SY5Y. Interestingly, we show that resistin treatment completely abolished adiponectin-dependent Akt phosphorylation whereas ERK1/2 was not affected. Importantly, resistin treated SH-SY5Y cells showed a marked down-regulation of adiponectin receptor (AdipoR1) and APPL1, a critical mediator of both adiponectin and insulin signaling. This has been confirmed *in vivo*. Indeed, in Wistar rats, chronic ICV resistin infusion (14 days) markedly reduced hypothalamic expression of APPL1 AdipoR1 and AdipoR2. Furthermore, to assess whether resistin action on adiponectin signalling is mediated by TLR4, we generated TLR4-depleted SH-SY5Y cells. Interestingly, the knock-down of TLR4 completely abrogates the resistin-dependent down regulation of AdipoR1 and APPL1 and totally restablished adiponectin-dependent phosphorylation of AKT. Collectively, these results indicate that resistin-dependent activation of TLR4 promotes the down regulation of APPL-1 and adiponectin receptors leading to the alteration of adiponectin signalling. This could contribute, at least in part, to the impairment of the insulin-sensitizing effect of adiponectin at the neuronal level.
Disclosure
This work was supported by funds from university Paris Sud and CNRS (Centre National de la recherche Scientifique), France.

DOI: 10.1530/endoabs.37.OC10.1

OC10.2

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

Hamza Amine[1,2], Yacir Benomar[1,2], Nadia Meskini[3] & Mohammed Taouis[1,2]
[1]Neuroendocrinologie Moléculaire de la Prise Alimentaire, University of Paris-Sud, UMR 9197, Orsay, France; [2]Neuroendocrinologie Moléculaire de la Prise Alimentaire, Neuroscience Paris Saclay Institute, CNRS UMR 9197, Orsay, France; [3]Nutrition, Environment and Health Laboratory, University Hassan II, Casablanca, Morocco.

Omega-3 polyunsaturated fatty acids modulate the risk factors for metabolic syndrome via multiple mechanisms. However, their underlying mechanisms on insulin resistance and type 2 diabetes are still unknown. Here, we report that Odontella aurita, a microalga rich in the omega-3 polyunsaturated fatty acid eicosapentaenoic acid (EPA), prevents high saturated fat diet induced insulin resistance and inflammation in the liver of Wistar rats. High fat diet (HFD), given for 8 weeks, increased plasma insulin levels associated with the down-regulation of insulin receptor (IR) and the impairment of insulin-dependent IR phosphorylation. Furthermore, HFD increased toll-like receptor 4 (TLR4) expressions. Indeed, we have recently reported that TLR4 is implicated in resistin-induced inflammation and insulin resistance in the hypothalamus.[1] We also show that TLR-4 up-regulation is concomitant with the activation of c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (p38). Importantly, Odontella aurita enriched HFD (HFOA, 12%) normalized body weight and plasma insulin levels, and restores IR expression at both protein and mRNA levels. In addition, HFAO improves insulin responsiveness as estimated by *in vitro* phosphorylation of hepatic plasma membrane IR. Furthermore, HFOA decreased TLR4 expression and JNK/p38 phosphorylation. In conclusion, we demonstrate, for the first time to our knowledge, that omega-3 fatty acids brought by Ondontella aurita overcomes HFD-induced insulin resistance through the inhibition of TLR4/JNK/p38 MAP kinase signaling pathways.

Disclosure
This work was supported by funds from University of Paris Sud and the CNRS (centre nationale de la recherche scientifique, France).

Reference

1. Benomar Y, Gertler A, De Lacy P, Crépin D, Ould Hamouda H, Riffault L & Taouis M. Central resistin overexposure induces insulin resistance through Toll-like receptor 4. *Diabetes* 2013 **62** 102–114.

DOI: 10.1530/endoabs.37.OC10.2

OC10.3

The thyroid hormones antagonize TGFβ responses suppressing fibrosis

Elvira Alonso-Merino[1], Rosa M Martín Orozco[1], Lidia Ruiz Llorente[1], Olaia Martínez-Iglesias[1], Juan P Velasco-Martín[2], Luisa F Fanjul-Rodríguez[1], Javier Regadera[2] & Ana Aranda[1]
[1]Instituto de Investigaciones Biomédicas Alberto Sols CSIC-UAM, Madrid, Spain; [2]Departamento de Anatomía, Histología y Neurociencia, Facultad de Medicina, UAM, Madrid, Spain.

Fibrosis represents a major health concern and presently has no successful treatment. Chronic liver fibrosis leads to portal hypertension, cirrhosis, hepatocellular carcinoma and liver failure. Transforming growth factor β (TGFβ), the main profibrogenic factor, mediates its actions mainly through activation of Smad transcription factors. We have previously observed a cross-talk between the thyroid hormone receptors (TRs) and the TGFβ pathway by which the thyroid hormone-bound TRs can antagonize TGFβ-mediated responses. Here, we demonstrate the functional importance of this antagonism *in vivo* using a mouse model of hepatic fibrosis induced by CCl4, a widely used hepatotoxic agent. In normal mice, acute treatment (48 h) with CCl4 caused significant necrosis with nuclei loss of hepatocytes surrounding centrilobular veins, while this was not observed in hyperthyroid mice. Concomitantly, induction of Smad2 phosphorylation in response to CCl4 was markedly blunted in the hyperthyroid animals, showing that the thyroid hormones reduce activation of the TGFβ pathway *in vivo*. Moreover, after chronic exposure to CCl4, the hyperthyroid animals developed a less severe liver fibrosis, with less Collagen 1 deposition and significantly reduced expression of α-SMA, the main marker of myofibroblast activation. The mRNA levels of *Col1a1*, *Col1a2* and *α-Sma* in response to CCl4 were also lower in the hyperthyroid mice. Furthermore, fibrosis appeared spontaneously in livers of 18-month-old mice in which TRs have been genetically ablated, thus implicating these receptors as physiological negative regulators of the fibrotic response *in vivo* in this organ. These finding define a novel function of the thyroid hormone receptors, and suggest that development of novel TR ligands capable of disrupting TGFβ/SMAD activity could constitute a novel therapeutic approach to block the progression of fibrotic diseases.

Disclosure
BFU2011-28058 from Ministerio de Economía y Competitividad; S2011/BMD-2328 TIRONET, from the Comunidad de Madrid and RD12/0036/0030 from the Instituto de Salud Carlos III.

DOI: 10.1530/endoabs.37.OC10.3

OC10.4

An autoregulatory loop of nuclear corepressor 1 expression controls hepatocarcinoma invasion, growth and metastasis

Olaia Martinez-Iglesias[1], Elvira Alonso-Merino[1], Juan P Velasco-Martín[2], Rosa M Martín-Orozco[1], Enrique Luengo[1], Rosa M García-Martín[3], Inmaculada Ibanez de Caceres[4], Agustin F Fernández[5], Mario Fraga[5], Pilar Gonzalez-Peramato[6], Constantino Varona[7], Jose Palacios[7], Javier Regadera[2] & Ana Aranda[1]
[1]Instituto de Investigaciones Biomédicas 'Alberto Sols', Consejo Superior de Investigaciones Científicas, Universidad Autónoma de Madrid, Madrid, Spain; [2]Departamento de Anatomía, Histología y Neurociencia, Facultad de Medicina, Universidad Autónoma de Madrid, Madrid, Spain; [3]Departamento de Anatomía Patológica, Hospital Universitario 12 de Octubre, Madrid, Spain; [4]Epigenetics Laboratory, INGEMM, Biomarkers and Experimental Therapeutics in Cancer, IdiPAZ, University Hospital La Paz, Madrid, Spain; [5]Instituto Universitario de Oncología del Principado de Asturias, Universidad de Oviedo, Oviedo, Spain; [6]Departamento de, Anatomía Patológica, Hospital Universitario La Paz, Madrid, Madrid, Spain; [7]Departamento de Anatomía Patológica. Hospital Universitario Ramón y Cajal, Madrid, Spain.

Nuclear corepressor 1 (NCoR) associates with nuclear receptors and other transcription factors leading to transcriptional repression. Genomic studies have shown the presence of inactivating mutations of the *NCoR* gene in human tumours and we have found that NCoR depletion with siRNA in hepatocarcinoma SK-hep1 cells enhances invasion, tumour growth and metastasis in nude mice, while expression of the thyroid hormone receptor β (TRβ) increases NCoR levels, repressing tumorigenesis. We have now analysed human hepatocarcinomas, finding that NCoR expression is significantly downregulated and that there is a good correlation with TRβ in the tumours, indicating the relevance of these observations in the patients. Strikingly, up to one month after siNCoR transfection, *NCoR* mRNA was still depleted in cells and tumours. This long-term depletion cannot be explained by DNA methylation of the regulatory CpG island of the *NCoR* promoter. In contrast, in chromatin immunoprecipitation (ChIP) assays we found increased recruitment of the corepressor SMRT and histone deacetylase 3 (HDAC3), as well as increase of the repressive histone marks H3K9me3 and H3K27me3. H3K9 methylation led to recruitment of the heterochromatin protein HP1γ, local heterochromatinisation, and exclusion of the stimulatory transcription factor SP1 from the promoter. Treatment of silenced cells with TSA, a HDAC inhibitor, caused *NCoR* gene re-expression, demonstrating the important role of histone deacetylation in long-term silencing of the *NCoR* gene. In conclusion, our data define NCoR as a potent tumour suppressor and as a potential therapeutic target in hepatocarcinomas. Our results also suggest that in the absence of *NCoR* mutations, a reduction of NCoR levels at a given point in time could be propagated for several generations to the daughter cells, enhancing their tumourigenic, invasive and metastatic capacity and contributing to tumour progression.

Disclosure
BFU2011-28058 from Ministerio de Economía y Competitividad; S2011/BMD-2328, from the Comunidad de Madrid and RD12/0036/0030 from the Instituto de Salud Carlos III and an AECC contract.

DOI: 10.1530/endoabs.37.OC10.4

OC10.5

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

Justyna Kulpa[1], Xiaofeng Wang[3], David Laperrière[1,2], Karine Audette[1,2], Jean Duchaine[1,2] & Sylvie Mader[1,2]
[1]Institute for Research in Immunology and Cancer, Montreal, Quebec, Canada; [2]Universite de Montreal, Montreal, Quebec, Canada; [3]Institute de Recherche Clinique de Montreal, Montreal, Quebec, Canada.

Over 70% of breast tumours express oestrogen receptor alpha (ERa). Stimulation with oestradiol results in receptor binding to oestrogen response elements (ERE)

in target gene regulatory sequences in association with transcription cofactors, and altered gene expression, resulting in proliferation and tumour growth. Our study aimed to systematically identify genes contributing to ER signalling and oestrogen-dependent proliferation in breast cancer. A genome-wide screen for genes affecting ER signalling was undertaken using a human ER(+) luminal breast cancer cell line (T47DKBLuc) stably expressing a luciferase reporter downstream of three EREs. Stimulation with oestradiol results in a profound increase in luciferase reporter expression, which can be consistently knocked down with shER. Using the Mission shRNA lentiviral library, three shRNA clones were produced for each of >16 000 genes. Following four days of lentiviral infection and oestradiol stimulation, reporter cells were screened for luciferase activity. Primary screening identified 1033 genes (double-hits; 60% cut-off) regulating luciferase reporter expression. We also identified 62 genes (double-hits, 25% cut-off) directly affecting cellular growth. Our hit list includes both known and potentially novel regulators of ER signalling and/or expression. A subset of 614 genes was selected for confirmatory and counter-screening using oestrogen-sensitive (T47DKBLuc, MCF7-ERE-Luc) and insensitive control (T47D-ARE-Luc and MCF7-ARE-Luc; antioxidant response reporter) cells, as well as for assessment of cell proliferation. Using Ingenuity Pathway Analysis (IPA) we confirmed that our screen identified many genes known to be involved in the canonical ER-signalling pathway. In addition, we identified genes involved in other canonical pathways including G-protein coupled receptor signalling, PI3K signalling, and signalling by nuclear receptors glucocorticoid receptor (GR) and androgen receptor (AR), amongst others. This study provides a wealth of data that will give insight into important factors affecting ER biology and proliferation of ER(+) tumours, and reveals potential targets for the treatment of this subclass of breast cancer.

DOI: 10.1530/endoabs.37.OC10.5

Obesity

OC11.1

Central resitin infusion impairs FGF21/FGFR1/β-Klotho hypothalamic expression and promotes peripheral FGF21 resistance: involvement of resistin/TLR4 signalling pathway

Yacir Benomar[1,2], Hamza Amine[1,2], Arieh Gertler[3] & Mohammed Taouis[1,2]
[1]Molecular Neuroendocrinology of Food Intake, UMR 9197, University Paris Sud, Orsay, France; [2]Molecular Neuroendocrinology of Food Intake, Neuroscience Paris-Saclay Institute, CNRS UMR 9197, University Paris Sud, Orsay, France; [3]Faculty of Agricultural, Food and Environmental Quality Sciences, The Institute of Biochemistry, Food Science, and Nutrition, The Hebrew University of Jerusalem, Rehovot, Israel.

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

Disclosure

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

DOI: 10.1530/endoabs.37.OC11.1

OC11.2

Serum glypican-4 levels and its association with cardiovascular risk predictor in women with polycystic ovary syndrome and healthy controls – pilot study

Andrzej Milewicz[1], Justyna Kuliczkowska-Plaksej[1], Agnieszka Lenarcik-Kabza[1], Anna Trzmiel-Bira[1], Lidia Hirnle[1], Urszula Zaleska-Dorobisz[1], Felicja Lwow[2], Lukasz Laczmanski[1], Katarzyna Kolackov[1], Natalia Sloka[1] & Diana Jedrzejuk[1]
[1]Univeristy of Medicine, Wroclaw, Poland; [2]University School of Physical Education, Wroclaw, Poland.

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

DOI: 10.1530/endoabs.37.OC11.2

OC11.3

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

Nur Izah Ab Razak[1,2], Scott MacKenzie[1], Louise Diver[1], Martin McBride[1] & Eleanor Davies[1]
[1]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, Scotland, UK; [2]Faculty of Medicine & Health Sciences, University Putra Malaysia, Serdang, Selangor, Malaysia.

Inappropriately high secretion of aldosterone can lead to hypertension and its various cardiovascular consequences. We previously showed that microRNA (miRNA) plays a significant role in the regulation of aldosterone biosynthesis. In this study we measured miRNA levels in H295R cells, the most commonly-used human adrenocortical cell line, and investigated how these change in response to the stimulation of aldosterone biosynthesis.

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

Disclosure
Ministry of Education, Malaysia.
DOI: 10.1530/endoabs.37.OC11.3

OC11.4

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

Jan Scholte[1], Anton Scheurink[1], Thierry Abribat[2], Michel Julien[2], Axel Themmen[3], AJ van der Lely[3] & Patric Delhanty[3]
[1]University of Groningen, Groningen, The Netherlands; [2]Alizé Pharma, Lyon, France; [3]Erasmus MC, Rotterdam, The Netherlands.

The peptides acylated and unacylated ghrelin (AG and UAG) are produced predominantly in the stomach. AG is the only known circulating orexigenic hormone with obesogenic and insulin-desensitising properties. Recent evidence suggests that UAG can inhibit these activities of AG. To investigate potential inhibitory effects of UAG and AZP-531, a UAG analogue, on AG-induced appetite and obesity we used an established rat model of diet induced obesity. Animals were fed a high-fat diet, then at 3 weeks implanted with osmotic mini-pumps containing either vehicle, AG, UAG, AG+UAG, AZP-531 or AG+AZP-531 ($n=8$ per group). All peptides were infused at 4 nmol/kg per h for 4 weeks. From 1 week before the start of infusion body weight and food intake were measured daily, blood sampling and assessments of feeding behaviour were made weekly. At the end of the experiment fat mass of different tissues, and body water and lean mass were measured. Tissues were also processed for mRNA analysis. The AG treated groups showed increased weight gain relative to the non-AG treated groups, but there was no significant effect of the UAG analogues. AG significantly increased total fat, but not lean or water mass. Remarkably, UAG and AZP-531 blocked AG-induced total fat accumulation, their inhibitory effects being localised to subcutaneous and retroperitoneal depots. UAG and AZP-531 also significantly suppressed AG-driven total food intake as well as aspects of AG-driven feeding behaviour, particularly speed of food intake. These activities may occur via a central mechanism since UAG and AZP-531 prevented the suppression of hypothalamic *Mc4r* mRNA by AG. In conclusion, UAG analogues suppress AG-induced fat accumulation and feeding behaviours, and may therefore have therapeutic potential in clinical indications where hyperphagia and altered behaviour towards food are related to high ghrelin levels such as Prader-Willi syndrome.

DOI: 10.1530/endoabs.37.OC11.4

OC11.5

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

Ivan Dedov[1,2], Galina Melnichenko[1,2], Tatiana Romantsova[2] & Marina Zhuravleva[2]
[1]Endocrinology Research Center, Moscow, Russia; [2]I.M. Sechenov Moscow State Medical University, Moscow, Russia.

Background
The SCOUT trial showed that sibutramine produced weight loss with some increased cardiovascular morbidity but not mortality. But these results should not be extrapolated to a routine practice as a lot of the SCOUT participants had contraindications for sibutramine. In order to summarise data on efficacy and safety of sibutramine administration in routine clinical practice according to approved indications and to implement risks monitoring system in Russia, PRIMAVERA non-interventional study has been initiated (NCT01773733, clinicaltrial.gov).
Methods
98.774 obese patients from 142 Russian cities, treated with sibutramine 10–15 mg/day. Preliminary results were analyzed for 16 515 patients (82% – women, 18% – men). Patients were treated under control of body weight, blood pressure and pulse rate.
Results
2.5% of patients dropped out during screening phase due to contraindications to sibutamine use. 3% of patients stayed on treatment for 3 month, 65% – for 6 month and 29.5% – for 12 month. Mean weight loss was significant: 7.5 ± 2.8 kg by month 3, 14.3 ± 5.9 kg by month 6 and 18.8 ± 8.2 kg by month 12 ($P<0.01$). Mean waist circumference decreased significant: 5.85 ± 3.31 cm, 10.71 ± 6.48 cm and 15.15 ± 8.91 cm by month 3, 6 and 12 respectively ($P<0.01$). According to the Well-Being Questionnaire, body weight loss was accompanied by general increase in quality of life. Treatment with sibutramine was not associated with significant increase of blood pressure and pulse rate. Adverse events were reported for 2.8% patients. There were no reports of The Serious Adverse Events related to sibutramine use.
Conclusion
Based on preliminary analysis, sibutramine use according to approved indications is safe and effective for long-term treatment of obesity. Due to PRIMAVERA program the principles of sibutramine efficacy and safety monitoring are being implemented into routine clinical practice.
Disclosure
The research was supported by 'Promomed RUS' pharmaceutical company.
DOI: 10.1530/endoabs.37.OC11.5

Pituitary - Clinical

OC12.1

The Irish TSHoma study: a multicentre retrospective study

Agnieszka Pazderska[1], Martin Cuesta[2], Helen Wallace[3], Audrey Melvin[4], James Gibney[1], Amar Agha[2], Donal O'Halloran[4], Steven Hunter[3], Chris Thompson[2] & Mark Sherlock[1,5]
[1]Department of Endocrinology, Adelaide and Meath Hospital Incorporating the National Children's Hospital, Tallaght, Dublin 24, Ireland; [2]Department of Endocrinology, Beaumont Hospital, Dublin 9, Ireland; [3]Department of Endocrinology, Royal Victoria Hospital, Belfast, UK; [4]Department of Endocrinology, Cork University Hospital, Cork, Ireland; [5]Department of Endocrinology, Trinity College Dublin, Dublin, Ireland.

TSH-secreting pituitary adenomas (TSHomas) are rare. Previously, the reported prevalence was one case per million populations although this is probably an underestimate. A recently published study reported a prevalence of TSHomas in Sweden of 2.8/million inhabitants.
Methods/design
Observational study conducted in four tertiary referral centres in Ireland. We retrospectively collected data on the prevalence, demographics, hormonal profile, tumour characteristics, and treatment outcomes for patients with TSHomas.
Results
21 patients (eight males) were diagnosed with TSHoma between 1968 and 2014. Mean age at diagnosis was 46 years. The prevalence of TSHomas in Ireland (Republic of Ireland and Northern Ireland) is 3.3/million inhabitants. This may be an underestimate as other centres may have TSHomas that were not included. At diagnosis, the median free thyroxine was 49.9% (IQR 50.3%) above the upper reference range. Eleven patients (52%) had TSH within normal range at diagnosis. 5/21 (23.8%) patients co-secreted GH and 4/21 (19%) patients had elevated prolactin. The median adenoma size was 13.5 mm (IQR 18.7) and 12/21 patients had a macroadenoma.15/21 patients were treated with surgery (two required craniectomy) as a primary therapy, 6/21 were treated with a somatostatin receptor ligand (SRL), five as a primary therapy. Somatostatin analogues normalised thyroid function in 4/5 patients. 8/21 patients underwent radiotherapy for either persistent active disease or tumour growth. 4/21 had hormonally active disease at the last follow up; three of these were treated with transsphenoidal surgery and radiotherapy and one with SRL. 11/21 (52%) had other pituitary hormones deficiencies at the most recent follow up.
Conclusion
The prevalence of TSHoma in Ireland exceeds the previously cited estimate of one case per million. Multimodal treatment is often required to normalise thyroid function and prevent tumour growth.

DOI: 10.1530/endoabs.37.OC12.1

OC12.2

The ubiquitin-specific protease 8 gene is frequently mutated in adenomas causing Cushing's disease

Luis Gustavo Pérez Rivas[1], Marily Theodoropoulou[2], Francesco Ferraù[3], Clara Nusser[1], Kohei Kawaguchi[4], Constantine Stratakis[5], Fabio Rueda Faucz[5], Luiz Eduardo Wildemberg[6], Guillaume Assié[7], Rudi Beschorner[8], Günther Stalla[2], Michael Buchfelder[10], Vera Popovic[11], Jürgen Honneger[9], Jerôme Bertherat[7], Monica R Gadelha[6], Felix Beuschlein[1], Masayuki Komada[4], Márta Korbonits[3] & Martin Reincke[1]
[1]Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Munich, Bavaria, Germany; [2]Department of Endocrinology, Max Planck Institute of Psychiatry, Munich, Bavaria, Germany; [3]Barts and The London School of Medicine, William Harvey Research Institute, Centre for Endocrinology, Queen Mary University of London, London, UK;

[4]Department of Biological Sciences, Tokyo Institute of Technology, Yokohama, Japan; [5]Section on Endocrinology and Genetics, Program on Developmental Endocrinology and Genetics, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA; [6]Division of Endocrinology, Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil; [7]INSERM Unité 1016, Centre National de la Recherche Scientifique Unité Mixte de Recherche, Institut Cochin, Université Paris Descartes, Paris, France; [8]Department of Neuropathology, Institute of Pathology and Neuropathology, Tübingen, Baden-Wurtemberg, Germany; [9]Department of Neurosurgery, Eberhard Karls University Tübingen, Tübingen, Baden-Wurtemberg, Germany; [10]Neurochirurgische Klinik, Klinikum der Universität Erlangen, Erlangen, Bavaria, Germany; [11]Clinic of Endocrinology, Diabetes and Metabolic Diseases, Faculty of Medicine, University of Belgrade, University Clinical Center Belgrade, Belgrade, Serbia.

We have recently reported that somatic mutations in the ubiquitin-specific protease 8 (USP8) are present in corticotropinomas of patients with Cushing's disease and that these mutations reduced the interaction with 14-3-3. Mutant USP8 exhibited higher deubiquitination activity and potentiated EGFR-induced POMC expression (Reincke *et al*., *Nat Genet* 2014). To further study the prevalence of these mutations, we have analyzed 134 ACTH-producing corticotropinomas of patients with diagnosed Cushing's disease from eight different centers by Sanger sequencing.

Results

Somatic mutations in USP8 were found in 48 cases (37%), but not in an additional cohort of 11 'silent' corticotropinomas. The center-specific prevalence ranged from 10.5 to 57% and was lower in pediatric patients (17% vs 41%; $P<0.05$). Adults having adenomas with USP8 mutations were diagnosed at earlier age (36 years vs 44 years; $P<0.05$) and had a higher BMI than those with wild type adenomas. Mutations were more frequent in females than in males (43% vs 17%; $P<0.005$) and were mainly found in adenomas of intermediate size (11.9 ± 6.3 mm). Patients with adenomas containing USP8 mutations also tended to have lower preoperative hormonal levels, although the differences were not significant, and were less prone to develop adrenal insufficiency postoperatively than those with WT tumors (49% vs 71% respectively; $P<0.05$). Mutations affected the residues Ser718 (52%) or Pro720 (48%). In addition, we identified five new alterations: one missense substitution and four in-frame deletions of several amino acids. They reduced the interaction between USP8 and 14-3-3, increased USP8 cleavage and enhanced its activity. USP8 mutants diminished EGFR ubiquitination and consequently impaired its lysosomal degradation. Furthermore, mutant USP8 proteins enhanced EGFR-induced POMC promoter activity in immortalized AtT20 corticotropinoma cells.

In conclusion, our data highlight the prevalence of USP8 mutations in Cushing's disease and link these alterations to female adult patients with younger age.

Disclosure

The study was supported by the Else Kröner-Fresenius-Stiftung (grant number 2012_A103 to M Reincke) and the Ministry of Education, Culture, Science and Technology of Japan (grant number 24112003 to M K). M Theodoropoulou is supported by the German Federal Ministry of Education.

DOI: 10.1530/endoabs.37.OC12.2

OC12.3

The genetic causes of pituitary gigantism

Liliya Rostomyan[1], Adrian Daly[1], Patrick Petrossians[1], Giampaolo Trivellin[2], Nalini Shah[3], Giovanna Mantovani[8], Sebastian Neggers[4], Emilie Castermans[7], Jean-Hubert Caberg[9], Philippe Chanson[6], Sabina Zacharieva[5], Luciana Naves[10] & Albert Beckers[1]
[1]Department of Endocrinology, CHU de Liège, University of Liège, Liège, Belgium; [2]NIH/NICHD, DEB, SEGEN, Bethesda, Maryland, USA; [3]Department of Endocrinology, King Edward Memorial Hospital, Mumbai, India; [4]Department of Endocrinology, Erasmus Medical Center, Rotterdam, The Netherlands; [5]Department of Endocrinology, Sofia Medical University, Sofia, Bulgaria; [6]Department of Endocrinology, Le Kermlin-Bicetre, Paris, France; [7]Department of Endocrinology, Hopsital Universitario La Paz, Madrid, Spain; [8]Department of Endocrinology, Fondazione Ospedale Maggiore Policlinico IRCCS, Milan, Italy; [9]Department of Clinical Genetics, CHU de Liège, University of Liège, Liège, Belgium; [10]Department of Endocrinology, University of Brasilia, Brasilia, Brazil.

Increased secretion of GH results in gigantism in children/adolescents and in acromegaly in adults; the relative roles of the various genetic causes of acromegaly and gigantism are still unclear. To analyse the genetic causes and inherited/familial features in patients with pituitary gigantism, we studied a large international cohort. Genetic or inherited characteristics were observed in 39% of patients and included familial isolated pituitary adenomas (FIPA; $n=28$), McCune–Albright syndrome ($n=7$), Carney complex ($n=2$), and MEN1 ($n=1$). Germline mutations in the AIP gene were found in 31% of tested cases; a microduplication at Xq26.3 was detected in two kindreds and ten sporadic patients with a novel pediatric onset gigantism syndrome, termed X-linked acromegigantism (X-LAG). AIPmut positive patients were almost all males (95%), whereas X-linked acrogigantism group (X-LAG) consisted mostly of females (71%). AIPmut positive and X-LAG patients had significantly younger ages at first symptoms (13.5 and 1.5 years) and at diagnosis (16.8 and 3 years) than AIP negative patients (15 and 24 years respectively). Among non-X-LAG patients none had grown excessively before the age of 5 years. Pituitary lesions were usually macroadenomas and their size was not different in AIPmut, AIPwt, and X-LAG groups. All patients had marked hypersecretion of GH/IGF1. Prolactin co-secretion was more frequent in X-LAG than in AIPmut cases.

Conclusions

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

DOI: 10.1530/endoabs.37.OC12.3

OC12.4

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

Marco Faustini-Fustini[1], Alberto Righi[2], Sofia Asioli[3], Luca Morandi[3], Matteo Zoli[1], Diego Mazzatenta[1], Giorgio Frank[1] & Maria Pia Foschini[3]
[1]IRCCS Istituto delle Scienze Neurologiche di Bologna (ISNB), Bellaria Hospital, Bologna, Italy; [2]Department of Pathology, Rizzoli Institute, Bologna, Italy; [3]Section of Anatomic Pathology, Department of Biomedical and Neuro Motor Sciences, Bellaria Hospital, Bologna, Italy.

Introduction

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

Methods/design

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

Results

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

Conclusion

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

DOI: 10.1530/endoabs.37.OC12.4

OC12.5

The clinical characteristics of X-linked acro-gigantism syndrome

Adrian Daly[1], Giampaolo Trivellin[2], Liliya Rostomyan[1], Bo Yuan[3], Catherine Choong[4], Jacques Young[5], Giovanna Mantovani[6], Luciana Naves[7], Philippe Lysy[8], Tim Cheetham[9], Nalini Shah[10], Daniel Metzger[11], Maria Chiara Zatelli[12], Natalia Strebkova[13], Nadia Mazerkina[14], Michael Collins[15], Maya Beth Lodish[2], James Lupski[3], Constantine Stratakis[2] & Albert Beckers[1]

[1]Department of Endocrinology, CHU de Liège, University of Liège, Liège, Belgium; [2]Program on Developmental Endocrinology and Genetics, Section on Endocrinology and Genetics, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health, Bethesda, Maryland, USA; [3]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas, USA; [4]Department of Pediatric Endocrinology and Diabetes, Princess Margaret Hospital for Children, Subiaco, Western Australia, Australia; [5]INSERM U693, GHU Paris-Sud, Hôpital de Bicêtre, Paris, France; [6]Endocrinology and Diabetology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; [7]Department of Endocrinology, University of Brasilia, Brasilia, Brazil; [8]Pediatric Endocrinology Unit, Université Catholique de Louvain, Brussels, Belgium; [9]Department of Paediatric Endocrinology, Royal Victoria Infirmary, Newcastle University, Newcastle-Upon-Tyne, UK; [10]Department of Endocrinology, KEM Hospital, Mumbai, India; [11]Endocrinology and Diabetes Unit, BC Children's Hospital, Vancouver, British Columbia, Canada; [12]Section of Endocrinology, Department of Medical Sciences, University of Ferrara, Ferrara, Italy; [13]Institute of Pediatric Endocrinology, Endocrinological Research Centre, Moscow, Russia; [14]Burdenko Neurosurgery Institute, Moscow, Russia; [15]Skeletal Clinical Studies Unit, National Institute of Dental and Craniofacial Research, NIH, Bethesda, Maryland, USA.

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

Disclosure

This work was supported by U.S. DHHS-NIH-NICHD (Z01-HD008920); U.S. Department of Health and Human Services-National Institutes of Health-National Human Genome Research Institute (U54HG006542); Fonds D'Investissement de Recherche Scientifique.

DOI: 10.1530/endoabs.37.OC12.5

Guided Posters

Adrenal

GP.01.01

Low-dose ACTH testing does not predict treatment response to corticosteroids in community-acquired pneumonia

Claudine A Blum[1,2], Philipp Schuetz[3], Nicole Nigro[1], Bettina Winzeler[1], Birsen Arici[1], Julie Refardt[1], Sandrine A Urwyler[1], Matthias Briel[1,4], Beat Mueller[3] & Mirjam Christ-Crain[1]
[1]Division of Endocrinology, Diabetology and Metabolism, Departments of Internal Medicine and Clinical Research, University Hospital Basel, Basel, Switzerland; [2]Service d'Accueil des Urgences, CHU Pitié-Salpêtrière et AP-HP, Paris, France; [3]Departments of Internal and Emergency Medicine and Department of Endocrinology, Diabetology and Clinical Nutrition, Medical University Clinic, Kantonsspital Aarau, Aarau, Switzerland; [4]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada.

Background
It is controversial whether the attenuated increase of circulating cortisol to ACTH stimulation predicts treatment response to corticosteroids in patients with critical illness. We investigated whether ACTH testing predicts treatment response to corticosteroids in patients with community-acquired pneumonia (CAP).
Methods
We performed a low dose (1 μg) ACTH test on admission in a prospective randomised, double-blind, placebo-controlled multicenter trial comparing prednisone 50 mg for 7 days to placebo in patients hospitalized with CAP. The results of the main study showed a benefit of corticosteroids in community-acquired pneumonia.[1] Cortisol was measured at baseline and 30 min after stimulation with 1 μg ACTH. We performed Cox regression models for time to clinical stability (TTCS) to compare baseline and stimulated cortisol levels between both treatment groups.
Results
348 patients in the prednisone group and 330 patients in the placebo group were evaluated. 176 patients in the prednisone group (50.6%) and 163 patients in the placebo group (49.4%) with a basal cortisol > median (751 nmol/l) had a significantly longer TTCS in both groups (4.4 days vs 2.1 days, $P<0.0001$ in the prednisone and 5.0 days vs 3.0 days in the placebo group, $P=0.0003$). Basal plasma cortisol levels did not predict treatment response to prednisone (P for interaction $=0.84$). Similarly, neither a delta cortisol <250 nmol/l after ACTH stimulation (P for interaction $=0.84$) nor the combination of basal cortisol and delta cortisol (P for interaction $=0.82$) predicted treatment response to corticosteroids.
Conclusion
Our data suggest that a low-dose ACTH test does not predict treatment response to corticosteroids in patients with CAP. This suggests a pharmacological effect of corticosteroids in patients with critical illness or CAP and argues against a critical illness-related corticosteroid insufficiency (CIRCI).
Reference
1. Blum CA *et al*. Lancet 2015 pii: S0140-6736 (14) 62447–62448 (Jan 16).
Disclosure
This work was supported by the Swiss National Science Foundation (grant numbers PP0P3_123346, P2BSP3_155212, PP00P3_150531/1, 320030-138267, and 320030-150025), the Nora van Meeuwen Häfliger Stiftung and the Gottfried Julia Bangerter-Rhyner Stiftung.
DOI: 10.1530/endoabs.37.GP.01.01

GP.01.02

Defining and exploring the excessive healthcare burden of adrenal insufficiency

Paul Stewart[1], Beverly M K Biller[2], Claudio Marelli[3], Candace Gunnarsson[4], Michael Ryan[4] & Gudmundur Johannsson[5]
[1]University of Leeds, Leeds, UK; [2]Massachusetts General Hospital, Boston, Massachusetts, USA; [3]Shire, Zug, Switzerland; [4]CTI Clinical Trial and Consulting, Cincinnati, Ohio, USA; [5]Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Göteborg, Sweden.

Introduction
The clinical outcome of patients with adrenal insufficiency (AI) has been shown to be less favorable than previously thought. Clinical studies have shown increased mortality, reduced cardiovascular and skeletal health and compromised quality of life, but the impact of this upon healthcare burden is unknown. This research utilised real-world evidence to compare comorbidities, healthcare utilization and expenditures in patients with AI.
Methods/design
Administrative health claims data from Truven Health MarketScan Commercial and Medicare databases (January 2006–June 2011) were used. Inclusion criteria were at least two diagnosis codes for AI and a minimum of 1 year of continuous health and pharmacy coverage following diagnosis. Patients were classified into cohorts of secondary AI (SAI) due to pituitary disorder ($n=1529$), primary AI (PAI) ($n=705$), and congenital adrenal hyperplasia (CAH) ($n=242$). Patients were matched 1:1 on age, gender, insurance type, and region to a general control population. Unadjusted average healthcare utilization and expenditures over 12 months are reported for each cohort and control. Multivariable models will be generated to estimate healthcare utilization and expenditures.
Results
All three groups showed higher relative risk of anxiety (SAI 1.87 (CI: 1.60, 2.18)); (PAI 1.89 (1.52, 2.35)); (CAH 2.14 (1.17, 3.94)); hypertension (SAI 1.25 (1.16, 1.35)); (PAI 1.15 (1.01, 1.32)); (CAH 1.60 (1.09, 2.35)); and diabetes mellitus (SAI 1.52 (1.31, 1.76)); (PAI 1.60 (1.24, 2.05)); (CAH 2.83 (1.50, 5.34)) than the general population. Depression (SAI 1.55 (1.39, 1.74)); (PAI 1.44 (1.23, 1.67)); and hyperlipidemia (SAI 1.36 (1.26, 1.47)); (PAI 1.23 (1.08, 1.41)); were higher in the SAI and PAI cohorts. Inpatient hospitalizations with infection were a frequent primary diagnosis for all three cohorts. Average total 12-month expenditures for each cohort compared to their matched controls were as follows: SAI = $29 628/control = $7044, PAI = $19 795/control = $5480, and CAH = $6145/control = $3542.
Conclusions
Patients with AI carry a significant healthcare burden with higher risk of comorbidities, hospital admissions and healthcare expenditures compared to the general population.
Disclosure
This work was funded by Shire International GmbH.
DOI: 10.1530/endoabs.37.GP.01.02

GP.01.03

Effect of the switch from conventional glucocorticoids to 'dual release hydrocortisone' in adult patients with primary and secondary adrenal insufficiency: a 6-month multicentre study

Rosario Pivonello[1], Chiara Simeoli[1], Andrea M Isidori[2], Alessandro Ciresi[3], Silvia Savastano[1], Renata S Auriemma[1], Chiara Graziadio[2], Carolina Di Somma[1], Carla Giordano[3], Andrea Lenzi[2] & Annamaria Colao[1]
[1]Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, Federico II University, Naples, Italy; [2]Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy; [3]Section of Endocrinology and Metabolic Disease, DIBIMIS, University of Palermo, Palermo, Italy.

Adrenal insufficiency (AI) requires life-long glucocorticoid (GC) treatment, which is associated with an increased risk of metabolic syndrome (MS), probably due to cortisol overexposure for multiple drug daily doses, together with an impairment of quality of life (QoL). Moreover treatment compliance (TC) is reported to be suboptimal in AI patients. The current study aimed at investigating the impact of the switch from twice/thrice daily conventional GCs to once daily dual-release-hydrocortisone (DR-HC) treatment on metabolic profile, QoL and TC in patients with primary AI (PAI) and secondary AI (SAI). Thirty-five patients (12 with PAI (7F, 5M, 33–60 years), eight treated with cortisone acetate (37.5–75 mg/day) and four with HC (20–30 mg/day)) and 23 patients with SAI (9F, 14M, 20–77 years), 15 treated with cortisone acetate (18.75–37.5 mg/day) and eight with HC (15–20 mg/day) entered the study and were evaluated before and 6 months after the switch to DR-HC (PAI: 20–60 mg/day and SAI: 20–40 mg/day). At 6-month-follow-up, in PAI patients, body weight (BW) ($P=0.036$) significantly improved and a trend to a significant improvement was also found for waist circumference (WC) ($P=0.086$). A diagnosis of MS, performed in two patients (17%) at baseline, was not confirmed after 6 months. In SAI patients, BW ($P=0.001$), BMI ($P=0.003$), and WC ($P=0.007$) significantly improved. A clear diagnosis of MS, performed in seven patients (30%) at baseline, was confirmed only in 4 (17%) of these patients after 6 months. In a subgroup of 12 patients with AI, visceral adiposity index (VAI), an indicator of adipose function and distribution, which seems to indirectly express the cardiometabolic risk, significantly improved ($P=0.05$) while an improvement in glucose levels ($P=0.064$) and in insulin sensitivity index (ISI 120) ($P=0.052$) was reported 120 min after glucose load. In the subgroup of ten patients considered for the evaluation of QoL and TC, working ability ameliorated in six patients (60%), vitality in 5 (50%), general health perception and depression in three patients (30%) and body pain perception in 2 (20%) patients. Moreover, 9 (90%) of these ten patients improved TC, changing from low to medium adherence. In conclusion, the switch from conventional GCs to DR-HC in patients with AI improved BW, BMI, WC, prevalence of MS, glucose tolerance and insulin sensitivity, QoL and TC.
DOI: 10.1530/endoabs.37.GP.01.03

GP.01.04

Clinical and genetic findings of an Italian series of patients with ACTH resistance syndromes

Marco Bonomi[1,2], Paolo Duminuco[2], Domenico Vladimiro Libri[2], Valeria Vezzoli[2], Alessandro Salvatoni[3], Valentino Cherubini[4], Anna Ficcadenti[5], Giorgio Radetti[6], Antonella Meloni[7] & Luca Persani[1,2]
[1]Dipartimento di Scienze Cliniche e di Comunità, Università degli Studi di Milano, Milano, Italy; [2]Divisione di Medicina ad Indirizzo Endocrino–Metabolico e Lab di Ricerche Endocrino–Metaboliche, IRCCS Istituto Auxologico Italiano, Milano, Italy; [3]Dipartimento di Pediatria, Università dell'Insubria, Ospedale Filippo del Ponte, Varese, Italy; [4]Ospedali Riuniti 'Umberto I – G.M.Lancisi – G.Salesi', SC Diabetologia Pediatrica, Ancona, Italy; [5]Clinica Pediatrica, Università Politecnica delle Marche, Ancona, Italy; [6]Ospedale Regionale di Bolzano, UO Pediatria, Bolzano, Italy; [7]UO DH II Clinica Pediatrica, Ospedale Microcitemico, Cagliari, Italy.

ACTH resistance syndromes (ARS) are rare, severe and heterogeneous diseases that include either familial glucocorticoid deficiency (FDG) or Allgrove syndrome (AS). FDG is a rare autosomal recessive disorder resulting from mutation in genes encoding either the ACTH-receptor (ACTHR) in FDG1, or its accessory protein MRAP, in FDG2. AS is characterized by adrenal insufficiency due to ACTH resistance, alacrimia, and achalasia secondary to mutations in the *AAAS* gene, which encodes a protein called ALADIN. Here we describe the clinical and genetic findings in six males with ARS (age at diagnosis: 2 days–14 years). Seizures, recurrent infection, hypoglycaemia, skin, and mucosal hyperpigmentation were common features, while achalasia and alacrimia were present in three patients, indicating AS. The genetic analyses of the three FGD patients were negative in one, but revealed a known causative heterozygous intronic variation (IVS 3ds+3insT) in MRAP in another one; and a known causative homozygous variation in ACTHR (p.Y254C), in association with two novel heterozygous non-synonimous SNPs in exons 2 and 3 of the MRAP, in the last patient. The molecular analysis of the three patients with AS showed: one known causative nonsense homozygous mutation (p.R194X) in the *ALADIN* gene in two brothers; in the last AS case, a novel homozygous intronic variant (IVS11–2) inherited from the two non-consanguineous heterozygous parents, both from Sardinia. This patient presented a congenital twisted feet and achalasia already at birth, but came to the diagnosis of AS only at the age of 14 years. The molecular characterisation of this novel variant, based on the mRNA analysis, demonstrated that it is affecting the splicing site of the exon 11 in *ALADIN* gene causing the formation of an aberrant protein with a premature stop codon. In conclusion, the frequency of FDG and AS in this short Italian series is similar, and we described a novel IVS in the Aladin gene that is causative for AS.

DOI: 10.1530/endoabs.37.GP.01.04

GP.01.05

Prevention of adrenal crisis in stress (The PACS Study): serum cortisol during elective surgery, acute trauma and sepsis in comparison to 'stress dose' hydrocortisone administration in adrenal insufficiency

Angela Taylor[1], Niki Karavitaki[2], David Smith[3], Irina Bancos[1], Mark Foster[4], Sibylle Meier[2], Donna O'Neil[1], John Komninos[2], Dimitra Vassiliadi[1], Christopher Mowatt[1], Janet Lord[4], John Wass[2] & Wiebke Arlt[1]
[1]Centre for Endocrinology, Diabetes and Metabolism, University of Birmingham, Birmingahm, UK; [2]Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK; [3]School of Mathematics, University of Birmingham, Birmingham, UK; [4]NIHR Surgical Reconstruction and Microbiology Research Centre, University of Birmingham, Birmingham, UK.

Patients with adrenal insufficiency require increased hydrocortisone (HC) replacement doses during surgery, trauma and infection to avoid life-threatening adrenal crisis. However, currently administered HC doses are chosen empirically rather than on rational grounds, with huge variability in administration modes, total dose and dosing intervals. To conclusively determine serum cortisol levels observed under stress conditions, we firstly collected blood samples from healthy controls ($n=86$), soldiers under combat stress ($n=105$) and patients undergoing elective surgery with general anaesthesia ($n=22$), acute major trauma ($n=85$), and severe sepsis ($n=100$). Secondly, we undertook frequent sampling over a period of 24 h in ten patients with primary adrenal insufficiency who omitted their regular replacement and received HC 200 mg/24 h in four different administration modes: 50 mg every 6 h orally or per i.m. or i.v. bolus injection or 200 mg/24 h as continuous i.v. infusion (IV-C). All analyses were carried out by liquid chromatography/tandem mass spectrometry. Serum cortisol concentrations were highest in patients with sepsis (median 973, range 77–7717 nmol/l), followed by elective surgery with general anaesthesia (617, 269–1379), combat stress (441, 69–789), acute trauma (235, 23–1257), and healthy controls (197, 67–752 nmol/l). Initial peak concentrations after HC exceeded stress levels, but serum cortisol decreased to under the median of controls several hours before repeat administration of oral, i.v., and i.m. bolus. By contrast, HC IV-C maintained steady state cortisol levels above the median of stressed controls throughout. Linear pharmacokinetic modelling combined with mixed effects regression calculated the optimal dose and administration mode as an initial bolus of 50–100 mg HC i.v., followed by continuous i.v. infusion of 200 mg/24 h. Continuous i.v. rather than bolus administration of HC will avoid dangerous intermittent trough levels and thus represents the recommended administration mode for patients with adrenal insufficiency exposed to pathological stress due to trauma, sepsis, or surgery.

DOI: 10.1530/endoabs.37.GP.01.05

GP.01.06

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

Manish Gutch[1], Sukriti Kumar[2], Syed Mohd Razi[1], Abhinav Gupta[1] & Keshav Kumar Gupta[1]
[1]LLRM Medical College, Meerut, Uttar Pradesh, India; [2]SGPGI, Lucknow, India.

Background
The hypothalamic–pituitary–adrenal axis has a pivotal role in combating acute insults. Glucocorticoids play a role directly or indirectly in the maintenance of normal vascular tone and in potentiating the vasoconstrictor action of catecholamine, associated with septic shock.
Aims
To determine the incidence of adrenal insufficiency (AI) and its relation to mortality in patients with septic shock.
Settings and design
A prospective observational study done at tertiary care centre.
Methods and materials
In patients of septic shock, APACHE II score was calculated and serum cortisol was measured at the time of admission and 1 h after giving 250 μg ACTH. Hydrocortisone was added to inotropics in all patients after drawing second blood sample for serum cortisol and was continued till 7 days or less. In our study, the patients with inadequate adrenal response were divided into two groups: i) absolute AI – baseline cortisol <20 μg/dl and increment ≤ 9 μg/dl after the ACTH stimulation test and ii) relative AI – patients with baseline cortisol ≥ 20 μg/dl and increment ≤ 9 μg/dl. Statistical analysis used: data were analysed with SPSS version 17 and were presented in the values of mean, median, and percentages. The P value of <0.05 was considered significant.
Results
The incidence of AI in septic shock was ($n=100$) was 42% (in absolute 14% and relative 28%). The incidence of AI in septic shock was 42% (absolute 14% and relative 28%). The mortality rate was 48%, and it was higher in patients with AI than in patients without AI ($P=0.017$). The APACHE II score >25 carried higher mortality rate than a score of <25 ($P\leq 0.001$). Baseline serum cortisol >45 μg/dl had exceptionally high likelihood of mortality (OR 50, $P\leq 0.001$). Among those who survived, inotropic support was required for longer period in relative as compared with absolute AI and to non-AI.
Conclusions
AI is prevalent among patients with septic shock. We found that higher APACHE scores were associated with higher rates of adrenal failure and mortality in patients with septic shock. There also appears to be a bimodal distribution of mortality with adrenal status in patients with septic shock.

DOI: 10.1530/endoabs.37.GP.01.06

GP.01.07

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

Cornelie Andela[1], Jitske Tiemensma[1,2], Nienke Biermasz[1], Johannes Romijn[3] & Alberto Pereira[1]
[1]Leiden University Medical Center, Leiden, The Netherlands; [2]University of California, Merced, California, USA; [3]Academic Medical Center, Amsterdam, The Netherlands.

Background
Hydrocortisone replacement for primary adrenal insufficiency (PAI) is targeted to mimic circadian endogenous cortisol secretion. Nevertheless, patients on stable

treatment report impairments in quality of life. The brain is a major target area for cortisol considering it high density of glucocorticoid receptors and previous studies in patients treated for Cushing's disease (CD) suggest that hypothalamic-pituitary-adrenal axis dysregulation is related to cognitive impairment.
Objective
To evaluate cognitive functioning in patients with PAI and to examine the possible effect of postponing early morning hydrocortisone intake. Furthermore, we aimed to assess cognitive functioning of patients with PAI relative to patients in remission of CD.
Patients and method
Cognitive functioning was measured in 31 patients with PAI and 31 healthy matched controls using eight neuropsychological tests, evaluating memory, verbal intelligence, and executive functioning. In addition, 29 patients were included who postponed their hydrocortisone intake to after the cognitive evaluation. Cognitive functioning scores of patients in remission of CD were obtained from previous research.
Results
Compared with controls, patients with PAI performed worse on auditory and visual memory tasks (all $P \leq 0.024$) and executive functioning tasks (all $P \leq 0.012$). In contrast, patients performed better on a concentration task ($P = 0.015$) and made less errors during a focused attention task ($P = 0.041$). No differences were observed between patients with and those that postponed hydrocortisone intake, except for fewer repeats during a verbal fluency task ($P = 0.025$) in patients that postponed hydrocortisone intake. Patients with PAI performed generally similar to patients in remission of CD (except for concentration and logical memory).
Conclusions
Patients on long-term hydrocortisone replacement for PAI demonstrate mild cognitive deficits compared with controls, and perform generally similar to patients in remission of CD. Future longitudinal studies are needed to provide more insight into the development and course of the observed cognitive alterations.

DOI: 10.1530/endoabs.37.GP.01.07

GP.01.08

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

Eesh Bhatia[1], Ghazala Zaidi[1], Aditya Sarangi[2], Vijayalakshmi Bhatia[1], Nisha Bharani[3], Alok Sachan[4], Li Zhang[5], Liping Yu[5], Vandana Jain[6], Saroj Sahu[1], Rashmi Srivastava[7], Niharika Bharti[1], Rakesh Aggarwal[2] & Amita Aggarwal[7]
[1]Department of Endocrinology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India; [2]Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India; [3]Department of Endocrinology, Amrita Institute of Medical Sciences, Kochi, India; [4]Department of Endocrinology, Sri Venkateshwara Institute of Medical Sciences, Tirupathi, India; [5]Department of Immunology, Barbara Davis Center for Childhood Diabetes, Denver, India; [6]Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India; [7]Department of Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Introduction
Autoimmune polyendocrine syndrome 1 (APS1) is an uncommon, serious autosomal recessive disorder, due to *AIRE* gene mutations which result in impaired central tolerance. India has a complex genetic structure and also communities with high prevalence of consanguinity, which may result in varied clinical manifestations and genetic mutations.
Aims
To study clinical features, interferon-α antibodies (IFNA), *AIRE* mutations, and *in-silico* functional analysis of novel mutations in Indian patients with APS1.
Patients and methods
Twenty patients (17 families) with clinical features of APS1 were studied. Nine patients previously reported by us (*Clin Genet* 2009 **76** 441) were included in the analysis. Clinical features (including mortality on follow-up), IFNA, bidirectional sequencing of *AIRE* gene, and i*n-silico* functional analysis of novel AIRE mutations were studied.
Results
Patients had three ($n = 9$), two ($n = 9$), or a single ($n = 2$, family members) major manifestation of APS1, in addition to various other organ-specific autoimmune disorders. On follow-up, mortality was high ($n = 6$, 30%), occurring at early age (5–23 years). IFNA was elevated with high titres in all patients, but was within normal range in family members with heterozygous mutations/WT sequence. Ten different mutations were detected, with C322fsX372 being most frequent (six families). Novel mutations included p.V80G ($n = 3$, in three different families from an in-bred community in Kerala, South India), p.L11P, p.C302X, and p.X546L + 59aa (c.1637G > T; terminal codon). The Finn-major mutation, R257X, was present in one patient. No specific genotype–phenotype correlation was observed. Functional analysis of two novel missense mutations (V80G and L11P) in the CARD domain revealed increased instability resulting from changes in intra-helical hydrogen binding.
Conclusions
Indian patients with APS1 syndrome had high mortality. IFNA was an inexpensive and sensitive marker for APS1. Multiple different *AIRE* mutations were present, including four novel mutations. Functional analysis of novel mutations revealed disruption of intra-helical hydrogen binding and increased instability.
Disclosure
This work was supported by an intra-mural research grant from Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

DOI: 10.1530/endoabs.37.GP.01.08

GP.02.01

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

Guido Di Dalmazi[1,2], Flaminia Fanelli[1,3], Marco Mezzullo[1,3], Elena Casadio[1], Eleonora Rinaldi[1], Silvia Garelli[1], Valentina Vicennati[1], Uberto Pagotto[1] & Renato Pasquali[1]
[1]Endocrinology Unit, Department of Medical and Surgical Sciences, Alma Mater University of Bologna, Bologna, Italy; [2]Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Munich, Germany; [3]Centro di Ricerca Biomedica Applicata (CRBA), Alma Mater University of Bologna, Bologna, Italy.

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

DOI: 10.1530/endoabs.37.GP.02.01

GP.02.02

Urinary glucocorticoid metabolites and adrenal incidentalomas?

Julie Brossaud[1,2], Dominique Ducint[1] & Jean-Benoît Corcuff[1,2]
[1]University Hospital, Bordeaux, France; [2]UMR 1286 INRA-Univ. Bordeaux, Bordeaux, France.

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

Design and patients
An inexpensive multiplex mass spectrometry assay was set up to quantify cortisol and its metabolites in 43 patients with benign secreting (AT+) or silent (AT−) adrenal tumours compared to 48 lean (Nl) or 143 obese (Ob) subjects, and to 26 patients with a Cushing's disease (CD). Their routine initial investigation included immunoreactive quantification of urinary free cortisol (UFC).
Results
Cortisol and metabolites were over-excreted in CD but not in Ob subjects. Nl and Ob were thus pooled in a control population (Ctl). Cortisol, tetrahydrocortisol (THF), and tetrahydrocortisone (THE) excretions were significantly increased in AT compared to Ctl subjects whereas immunoreactive UFC was similar. A logistic regression retaining cortisol, THF, and α- and β-cortolone as significant analytes allowed the construction of a receiver-operating characteristics (ROC) curve significantly better than the curve generated by cortisol alone (area under the curve (AUC) 0.927 vs 0.729, respectively, $P<0.0001$). More importantly, although there was no significant difference between Ctl vs AT− subjects for cortisol or metabolites a logistic regression retaining cortisol, alloTHF, and α- and β-cortolone as significant analytes generated a ROC curve performing significantly better than cortisol alone (AUC 0.910 vs 0.635, respectively, $P<0.0001$).
Conclusion
Cortisol and metabolites excretion is modified in AT, including AT−, patients even without modification of UFC. Clinical usefulness of these biomarkers has to be investigated in prospective studies following-up patients with AT.

DOI: 10.1530/endoabs.37.GP.02.02

GP.02.03

Differential expression of the PKA subunits in adrenocortical adenomas

Isabel Weigand[1], Cristina Ronchi[1], Davide Calebiro[2], Petra Rank[3], Sonja Steinhauer[1], Felix Beuschlein[3], Bruno Allolio[1], Martin Fassnacht[1] & Silviu Sbiera[1]
[1]University Hospital Wuerzburg, Wuerzburg, Bayern, Germany; [2]Univeristy of Wuerzburg, Wuerzburg, Bayern, Germany; [3]University Hospital Munich, Munich, Bayern, Germany.

Recently, mutations in the PRKACA (catalytic subunit α of the PKA) gene have been identified as causative in 35% of adrenocortical adenomas (ACA) with overt Cushing's syndrome (Beuschlein *et al*. 2014). These mutations lead to constitutive activation of PKA signaling and subsequently to an excessive production of cortisol. Protein kinase A is a heterotetramer consisting of two catalytic and two regulatory subunits with several isoforms (Cα, β, γ, RIα, IIα, Iβ, and IIβ). The stable tetramer is inactive, only upon cAMP induced dissociation of the regulatory subunits the active catalytic subunits are released. Here, we investigated the expression of the different PKA subunits in a large set of adrenal tumors. We performed immunohistochemistry staining of all PKA regulatory subunits and Cα on FFPE tissue from normal adrenal glands ($n=8$), ACA ($n=65$, 30 cortisol-producing/CPA, 17 aldosterone-producing, and 18 inactive) and adrenocortical carcinomas (ACC: $n=29$, seven cortisol-, three androgen-, 12 mixed hormone-producing, and seven inactive). Our results indicate a significantly decreased expression of RIIβ in CPAs, but only in the *PRKACA* mutated samples. A tendency for reduced expression under *PRKACA* mutation was also observed for RIα. No change in expression was found for the other two regulatory subunits or Cα. While reduced RIIβ expression in CPAs had previously been described (Mantovani *et al*. 2008), until now, this phenomena could not be linked to *PRKACA* mutational status. The former hypothesis that the decreased level of RIIβ leads by itself to the cortisol excess seems to be wrong, because RIIβ was not significantly changed in both ACA and ACC from patients with overt Cushing's syndrome but without *PRKACA* mutation. We therefore postulate that the reduced protein expression of RIIβ in CPA described earlier is a direct or indirect consequence of the newly identified mutation and not a general feature in CPAs. If this decrease arises post-transcriptionally or at transcriptional levels still needs to be elucidated.
Disclosure
This work was supported by the Deutsche Forschungsgemeinschaft (grant number: FA466/4-1 to M Fassnacht), IZKF Würzburg (grant number: B-281 to M Fassnacht), and the ERA NET 'E-rare' (grant number: 01GM1407B to M Fassnacht).

DOI: 10.1530/endoabs.37.GP.02.03

GP.02.04

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

Giuseppe Reimondo[1], Marcella Coletta[1], Giulia Peraga[1], Anna Pia[1], Micaela Pellegrino[2], Chiara Massaglia[1], Barbara Zaggia[1], Paolo Cosio[1], Elena Mbachu[1], Giorgio Borretta[2] & Massimo Terzolo[1]
[1]Internal Medicine I, Department of Clinical and Biological Sciences, San Luigi Hospital, University of Turin, Orbassano, Italy; [2]Endocrinology, Santa Croce e Carle Hospital, Cuneo, Italy.

Background
Adrenal incidentalomas are found in 3–7% of radiological series and many of them are adrenal adenomas. Autonomous cortisol secretion without clinical signs of overt hypercortisolism is a common finding in these patients. Studies reported metabolic derangement and increased cardiovascular risk associated with this state of subtle cortisol excess, however scanty data are available on the natural history of this condition.
Aim
To assess the rate of mortality in patients with incidentally discovered adenomas.
Methods
We studied 110 patients (39 males and 71 females) with incidentally discovered adrenal adenomas from 1998 to 2013. Metabolic and hormonal parameters were determined. We collected the following data: blood pressure, plasma glucose, lipid profile, cortisol levels after 1 mg dexamethasone suppression test (1 mg-DST), plasma ACTH, and urinary free cortisol. Mortality data were obtained from the demographic registers.
Results
Mean age of patients was 67 years, with a mean follow-up of 94 months. Fourteen (12.7%) patients died: 4 (28.6%) for cancer, 7 (50.0%) for cardiovascular, and 3 (21.4%) for respiratory/infective causes. Twelve of them (85.6%) had 1 mg-DST >1.8 μg/dl (four had hypertension, four dyslipidaemia, and four diabetes) while 54/96 patients alive at the last follow-up (56.2%) had 1 mg-DST >1.8 μg/dl ($P=0.04$). Survival probability was significantly reduced in patients with 1 mg-DST >1.8 μg/dl, with a hazard ratio of death of 3.64 (95% CI, 1.34–9.7; $P=0.013$). Age did not differ between patients alive or dead at the last follow-up (65.1±9.8 years vs 65.1±9.8 years, NS).
Conclusion
Patients with incidental adrenal adenomas and autonomous cortisol secretion heralded by cortisol after 1 mg-DST >1.8 μg/dl may be at increased risk of mortality compared to patients with non-secreting adenomas. Excess mortality is mainly related to cardiovascular events.

DOI: 10.1530/endoabs.37.GP.02.04

GP.02.05

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

Chiara Massaglia[1], Arianna Ardito[1], Barbara Zaggia[1], Vittoria Basile[1], Ettore Pelosi[2], Vincenzo Arena[2], Daniele Penna[2] & Massimo Terzolo[1]
[1]Internal Medicine 1, San Luigi Hospital, University of Turin, Orbassano, Italy; [2]IRMET, PET–CT Diagnostic Imaging Center, Turin, Italy.

Adrenocortical carcinoma (ACC) is a rare tumour characterised by a high rate of recurrence following radical surgery. Surgery of recurrent ACC may increase survival; thus, it is mandatory a timely and accurate detection of recurrence, either to increase the chance of radical extirpation or to avoid unnecessary surgery. This study investigated the role of PET–CT in the diagnosis of recurrence of ACC during follow-up of disease-free patients and analyzed whether this tool may improve the therapeutic strategy. A retrospective evaluation of the use of PET–CT was done in ACC patients with suspected recurrence at CT imaging during their follow-up. Data of 57 patients followed at our center were retrieved. Recurrence was confirmed by pathology when lesions were removed (23 cases), or fine-needle biopsy (five cases), or detection of unequivocal tumour progression during follow-up (29 cases). CT scan of the 57 patients showed a total of 153 lesions while PET–CT showed at least one focal uptake in 40 patients (70.2%) for a total of 99 lesions. For liver lesions, PET–CT showed a significantly higher specificity and a reduced sensitivity (sensitivity, CT 80% vs PET 50%, $P=0.046$ and specificity, CT 89% vs PET 99%, $P=0.057$). With regard to local recurrence, the two tests had similar diagnostic accuracy (sensitivity: CT 87% vs PET 79%, $P=$NS and specificity: CT 94% vs PET 94%, $P=$NS). The same considerations apply to abdominal recurrences (sensitivity: CT 76% vs PET 70%, $P=$NS and specificity: CT 94% vs PET 99%, $P=$NS) and bone, in which CT and PET have equal sensitivity (86%) and specificity (98%). Conversely, in the lungs CT scan had non-significantly better diagnostic accuracy (sensitivity: CT 87% vs PET 53%, $P=$NS and specificity: CT 91% vs PET 95%, $P=$NS). In 18 patients (33%),

PET findings changed the therapeutic strategy that was planned after CT as to the possibility of a radical surgery. In conclusion, PET can be considered an useful adjunct to CT for the diagnosis of ACC recurrence, increasing diagnostic specificity for suspected liver or abdominal recurrences, and improving the identification of occult lesions or multiple tumour sites. Use of PET has important clinical implications, allowing a smarter use of surgery due to improved selection of patients who can be radically resected.

DOI: 10.1530/endoabs.37.GP.02.05

GP.02.06

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

Eugenia Resmini[1,2], Alicia Santos[1,2], Anna Aulinas[1,2], Susan Webb[1,2], Beatriz Gómez-Anson[2,3], Olivia Cox[4] & Richard Lee[4]
[1]Endocrinology/Medicine Departments, Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBER-ER, Unidad 747), IIB-Sant Pau, ISCIII, Hospital Sant Pau, Barcelona, Spain; [2]Universitat Autònoma de Barcelona (UAB), Barcelona, Spain; [3]Neuroradiology Unit, Hospital Sant Pau, and IIB-Sant Pau, Barcelona, Spain; [4]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

Introduction
FKBP5 is a protein that regulates glucocorticoid receptor sensitivity, via an ultra-short negative feedback mechanism. Variations in the *FKBP5* gene can influence the response to glucocorticoids (GC). Hypercortisolaemia plays a role on impairment of brain function and could be mediated by epigenetic variations of the *FKBP5* gene. Cushing's syndrome (CS), a disease characterized by hypercortisolaemia, is associated with memory deficits, lower hippocampal volumes and a wide range of cognitive impairments. Recently, it has been demonstrated that GC-induced methylation changes in FKBP5 observed in blood DNA can serve as a proxy to both methylation and expression changes in the brain. We aimed at evaluating DNA methylation of FKBP5 in blood and its relationship with memory and hippocampal volumes (HV) in CS patients.
Patients and methods
33 CS patients with memory impairments (nine active and 24 cured) and 33 matched healthy controls were included. Memory tests, 3Tesla MRI of the brain, and DNA extraction from total leukocytes was carried out in all subjects. DNA from CS patients and healthy controls were bisulfite treated, PCR amplified, and pyrosequenced to assess a total of 34 CpG dinucleotides in introns 1, 2, and 5 of the *FKBP5* gene.
Results
We observed lower methylation in introns 2 and 5, in both cured and active CS patients compared to controls ($P<0.001$ and $P<0.05$ respectively). We also observed a positive correlation between the total methylation values and hippocampal volumes in active patients ($r=0.86$, $P<0.01$ left HV and $r=0.80$, $P=0.01$ right HV), but not with memory tests. However, there were multiple correlations between single CpG dinucleotides and memory test variables ($P<0.01$).
Conclusion
As lower DNA methylation in FKBP5 is associated with higher GC exposure and gene expression, our results demonstrate a relationship between blood DNA methylation and GC-induced brain impairments in CS patients.
Disclosure
This work was supported by Instituto de Salud Carlos III, Spanish Ministry of Science and Innovation (MICINN, FIS080302).

DOI: 10.1530/endoabs.37.GP.02.06

GP.02.07

Urinary free cortisone as a potential biomarker in diagnosing patients with mild Cushing's syndrome

Laura Trementino, Carolina Concettoni, Marianna Martino, Giorgia Marcelli, Grazia Michetti, Marco Boscaro & Giorgio Arnaldi
[1]Division of Endocrinology, Polytechnic University of Marche, Ancona, Italy; [2]Endocrinology Unit, Department of Medicine DIMED, University Hospital of Padua, Padua, Italy.

Introduction
Urinary free cortisol (UFC) determination has suboptimal sensitivity (SE) and specificity (SP) especially in mild Cushing's syndrome (CS).
Aim
To determine the performance of UFC and its metabolite cortisone (UFE) measured using accurate assays such as HPLC and LC–MS/MS in diagnosing patients with CS.
Patients and methods
Sixty-seven patients with CS were compared to 49 sex- and age-matched non-CS. UFF and UFE levels were assessed by HPLC until 2009 and afterwards by LC–MS/MS. The mean value of two 24-h urine collections was used for the analysis. SE and SP were calculated at different cut-off values using ROC curve analysis.
Results
UFF and UFE values were significantly higher in patients with CS. However, the diagnostic performance of UFF by HPLC was low with 75.8% SE and 81.1% SP (cut-off value >33.9 μg/24 h). The performance of UFF by LC–MS/MS was 88.2% SE and 91.2% SP (cut-off value >47.4 μg/24 h). The performance of UFE was better than UFF by both assays. UFE by LC–MS/MS showed 97.1% SE and 91.7 SP% using a cut-off value >88.7 μg/24 h. When CS patients were stratified according to disease severity, UFE by LC–MS/MS showed a good diagnostic profile also in mild CS (UFF $<2\times$ ULN) with 92.3% SE and 91.7% SP (cut-off value >88.7 μg/24 h). Conversely, the performance of UFF in mild CS was low (84.6% SE and 75% SP; cut-off value >44.2). UFF and UFE showed an optimal diagnostic performance with 100% SE and 100% SP in moderate to severe CS (UFF $\geq 2\times$ ULN). The performance of urinary steroids was not different according to age, sex, disease aetiology, and disease status in CS.
Conclusions
UFE measured by LC–MS/MS seems to be a new and good biomarker in diagnosing CS especially in patients with mild hypercortisolism at higher risk for misdiagnosis with UFF.

DOI: 10.1530/endoabs.37.GP.02.07

GP.02.08

ACTH-ectopic syndrome in four patients, caused by phaeochromocytoma

Eugenia Marova, Ludmila Rozhinskaya, Nikolay Kuznetsov, Anastasia Lapshina, Iya Voronkova, Svetlana Arapova, Galina Kolesnikova & Vadim Krylov
Endocrine Research Centre, Moscow, Russia.

Phaeochromocytomas are responsible for the development ACTH-ectopic syndrome in 5% cases. Less than 1% phaeochromocytoma accompanied by symptoms of ACTH-dependent hypercortisolism. We observed four cases of ACTH-secreting phaeochromocytoma during 2 years. All patients were women from 50 to 63 years. The disease duration ranged from 6 months to 5 years. The clinical picture presented the signs of hypercortisolism (matronism, hyperpigmentation of the skin, the redistribution of fatty tissue on the central type, and steroid myopathy) and hypercatecholaminaemia (arterial hypertension, tachycardia, shortness of breath, and frequent urination). Hormonal blood study found: morning ACTH 43.0–189.0 pg/ml (normal 7.0–66.0) evening 179.8–291.0 (normal 0–30.0), morning cortisol 962–4655 nmol/l (normal 123.0–626.0), evening 1256–2460 (normal 46.0–270.0), free cortisol in 24-h urine 3726.0–3828.0 nmol/day (normal 60.0–413.0); metanephrine in daily urine in three of four patients (638.0–1481.0 μg/day at the rate of 25.0–312.0) and normetanephrine (545.6–1553 μg/day at the rate of 35.0–445.0) (one patient had normal catecholamine levels). CT scans revealed tumors in the left adrenal glands sizes and density: $2.0\times1.6\times1.0$ cm (27H), $2.7\times3.0\times4.6$ cm (38H), and diameter 4.3 cm (density did not specified). In one case found two nodes: $1.8\times2.3\times2.5$ and $2.0\times2.3\times2.5$ cm (19H and 3H). Histological examination diagnosed three phaeochromocytoma combined with diffuse-nodular adrenal cortex hyperplasia and one mixed tumour (phaeochromocytoma and adenoma of the adrenal cortex). Immunohistochemical examination confirmed expression of ACTH in all cases. In all patients developed adrenal insufficiency and normalized levels of catecholamines after removal of adrenal tumors.
Conclusion
The diagnosis of ACTH-secreting phaeochromocytoma was established on the symptoms of hypercortisolism and hypercatecholaminaemia, excessive secretion of ACTH, cortisol and catecholamines in the blood and urine, the presence of neoplasms in the adrenal glands, the normalization of respective hormones after tumours removal, histological, and immuhistochemical confirmation of ACTH-secreting phaeochromocytomas.

DOI: 10.1530/endoabs.37.GP.02.08

GP.03.01

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

Ori Eyal[1,2], Anat Segev-Becker[1], Irit Ayalon[2], Anita Schachter-Davidov[1,2], Asaf Oren[1,2] & Naomi Weintrob[1,2]
[1]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [2]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel.

Background
Non-classical 21-hydroxylase deficiency (NC21OHD) is a mild form of congenital adrenal hyperplasia associated with different degrees of postnatal virilisation. Elevated serum androgen concentrations have been reported to be a risk factor for infertility, early pregnancy loss, and recurrent miscarriages in women with polycystic ovarian syndrome (PCOS).
Aims
The aim of this study was to assess time to conceive and pregnancy outcome in NC21OHD women in correlation with glucocorticoid (GC) therapy and androgen levels.
Patients and methods
We conducted a retrospective observational study in a tertiary medical centre. The outcome of 130 pregnancies among 59 women (mean age at diagnosis 20 ± 9.5 years and mean age at first pregnancy 29 ± 5years) with biochemical and genetic diagnosis of NC21OHD was reviewed. Androgen and 17OHP levels were measured before and during each trimester. The mean GC dose was 7.4 ± 3.3 mg hydrocortisone/m^2.
Results
There was no difference in time to conceive between pregnancies of women with and without treatment (7.7 ± 11 months vs 7.5 ± 25 months). There were 29 pregnancies without GC therapy and 101 with GC therapy. There was no significant difference between the rate of miscarriages between treated and untreated pregnancies (25% vs 17%, respectively, $P=0.6$). Birth weight was significantly lower in GC-treated pregnancies compared to untreated pregnancies (2.9 ± 0.4 kg vs 3.2 ± 0.5 kg, respectively, $P=0.03$). Androgen and 17OHP levels were similar in pregnancies that ended with miscarriage and those that ended with live birth.
Conclusions
Time to conceive is similar between treated and untreated pregnancies in NC21OHD women. In contrast to previous reports, there was no difference in miscarriage rates between treated and untreated pregnancies. There was significant decrease in birth weight in treated pregnancies despite the use of low doses of GC.

DOI: 10.1530/endoabs.37.GP.03.01

GP.03.02

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

Nayananjani Karunasena, Richard J Ross & Eleni Daniel
Academic Unit of Diabetes, Endocrinology and Metabolism, Department of Human Metabolism, University of Sheffield, Sheffield, UK.

Background
Androgens promote erythropoiesis and have been used for the treatment of anaemia. Furthermore, polycythemia is a known side effect of androgen therapy. In congenital adrenal hyperplasia (CAH), elevated adrenal androgens cause virilisation of female patients. Glucocorticoid treatment reduces androgen levels but there is a difficult balance between excess androgens and suppressed androgens due to excess glucocorticoid treatment.
Aim of study
To investigate the relationship between androgens and erythropoiesis in females with CAH.
Methodology
A retrospective case note review of 63 patients with CAH. Androgen levels and blood counts performed on the same day were collected and analysed in 44 patients; patients with medical conditions known to affect erythropoiesis were excluded.
Results
44 patients were studied (27 females); mean age was 35.5 ± 13.2 years. In women, there was a positive correlation of testosterone, androstenedione and 17-OHP levels with haemoglobin (Hb) and haematocrit (Hct).

Table 1 Correlations of Hb and Hct with androgens and 17-OHP in women.

	17-OHP	Androstenedione	Testosterone
Hb	$r=0.42$ ($P=0.0069$)	$r=0.4129$ ($P=0.0012$)	$r=0.4442$ ($P=0.0028$)
Hct	$r=0.3564$ ($P=0.024$)	$r=0.4346$ ($P=0.0006$)	$r=0.3673$ ($P=0.0154$)

There was a difference in Hb and Hct between patients with high, normal, and low androstenedione levels (ANOVA, $P<0.01$). Hct, but not Hb was significantly different with high, normal, and low testosterone levels (ANOVA, $P<0.01$). *Post hoc* analysis showed mean Hb and Hct levels were significantly different between high and low androstenedione and testosterone subgroups ($P=0.001$).
Conclusions
There is a positive correlation between adrenal androgens and erythropoiesis in women with CAH. This effect is significant not only at high levels of androgens but also at low levels. Suboptimal control of androgens in this group of patients may increase the risk of polycythemia and anaemia. Use of Hb and Hct as markers of disease control should be investigated in larger populations of CAH women.

DOI: 10.1530/endoabs.37.GP.03.02

GP.03.03

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

Kei Takase[1], Kazumasa Seiji[1], Ryo Morimoto[2], Yoshizugu Iwakura[2], Yoshikiyo Ono[2], Kei Omata[2], Masataka Kudo[2], Tomo Kinoshita[1], Fumitoshi Satoh[2] & Sadayoshi Ito[2]
[1]Department of Diagnostic Radiology, Tohoku University Hospital, Sendai, Japan; [2]Division of Nephrology, Endocrinology, and Vascular Medicine, Department of Medicine, Tohoku University Hospital, Sendai, Japan.

Purpose
To evaluate safety and efficacy of percutaneous radiofrequency ablation therapy for unilateral aldosterone producing adrenal adenoma in normalising aldosterone secretion.
Patients
Eight cases of aldosterone producing adrenal adenoma with following conditions: i) CT detectable adenoma without any risky organs on a puncture route. ii) Intervening adipose tissue between target adenoma and adjacent risky organs (pancreas or intestine). iii) Unilateral single functioning macroadenoma with aldosterone hypersecretion proven by adrenal venous sampling.
Methods
CT guided puncture of adrenal adenoma with one or two (according to the size of the adenoma) bipolar radiofrequency ablation needle was performed, followed by ablation with total power of 4–6 kJ. Blood pressure was monitored with an arterial catheter during the procedure. Aldosterone levels in serum and 24-h urine collection 7 days after ablation were evaluated as primary outcomes. ACTH, cortisol, serum aldosterone, renin activity, osmotic pressure, potassium level, urine osmolality, and antihypertensive medication dose at screening, 3, 7, 28, and 84 days after ablation therapy were also evaluated. Ablation effect was morphologically evaluated by enhanced CT 7 days after treatment.
Results
In all cases, aldosterone levels in serum and 24-h urine were significantly decreased; Serum potassium level was normalized without anti-aldosterone therapy. Postoperative CT showed complete ablation in six cases and subtle residual enhanced area in two cases. Doses of anti-hypertensive medication were reduced in all cases including two drug-free patients after ablation. No severe procedure-related complication was observed.
Conclusion
Bipolar radiofrequency ablation is thought to be safety and effective in treating primary aldosteronism.
Disclosure
Project of promoting innovative medidal devices by Ministry of Health, Labour and Welfar, Japan.

DOI: 10.1530/endoabs.37.GP.03.03

GP.03.04

Prolactinoma and primary aldosteronism: is there a causal link?

Tracy Ann Williams[1,2], Anna Dietz[1], Felix Beuschlein[1], Paolo Mulatero[2] & Martin Reincke[1]
[1]Ludwig-Maximillians-University-Munich, Munich, Germany; [2]University of Turin, Turin, Italy.

Introduction
We report the largest case series of concomitant prolactinoma and aldosterone-producing adenoma (APA), diagnosed in four patients from the German Conn Registry and in three patients at the Hypertension Unit, University of Torino. A disproportionate number (five out of seven) presented with macro-prolactinomas indicating that elevated prolactin (PRL) concentrations may play a role in APA formation. Further, increased expression of *PRLR* in the zona glomerulosa could sensitise the adrenal gland to the high circulating levels of PRL in prolactinoma patients.
Methods
PRLR gene expression data was from the GTEx Portal database2 (dbGaP accession number phs000424.vN.pN: www.gtexportal.org). Transcriptional profiles of eight APA and three normal adrenals were compared using an Affymetrix GeneChip HG-U133 Plus 2.0 gene expression platform. Effects of PRL were tested on *CYP11B2* gene expression levels and aldosterone production in NCI H295R cells.
Results
The uterus and the adrenal gland expressed the highest levels of the *PRLR* of the 45 tissues in the GTEx Portal database. Microarray analysis demonstrated a 1.55-fold upregulation of *PRLR* gene expression in APA compared to normal adrenals. In H295R cells PRL (100 nM) resulted in a 1.35 ± 0.02-fold upregulation in *CYP11B2* gene expression and a 1.26 ± 0.07-fold increase in aldosterone production.
Conclusion
High levels of PRL result in *CYP11B2* upregulation and an increase in aldosterone production *in vitro* and may play a role in APA development in cases of concomitant prolactinoma–APA.

DOI: 10.1530/endoabs.37.GP.03.04

GP.03.05

Short-term blood pressure response to mineralocorticoid-receptor blockade in aldosteronisms: primary hyperaldosteronism vs aldosterone-associated hypertension/low-renin hypertension

Irene Crespo[1], Teresa Ruiz-Gracia[1], Ana Ortolá[1], Emilia Gomez-Hoyos[2], Martin Cuesta[3], Ana Barabash[1], María Victoria Saez-de Parayuelo[1], Marisol Sanchez-Orta[1], Alfonso Calle-Pascual[1] & Isabelle Runkle[1]
[1]Hospital Clinico San Carlos, Madrid, Spain; [2]Hospital Clinico de Valladolid, Valladolid, Spain; [3]Beaumont Hospital, Dublin, Ireland.

Introduction
Some authors consider aldosteronism to be a spectrum, ranging from aldosterone-associated (or low-renin) hypertension (AAH) to primary hyperaldosteronism (PHA) due to bilateral adrenal hyperplasia. Thus, blood pressure (BP) response to mineralocorticoid-receptor blockade (MRB) could be similar.
Methods
Retrospective analysis of 60 patients. Screening per Endocrine Society guidelines, positive screening: aldosterone (pg/ml) to direct-renin (pg/ml) (ARR) ≥ 25. 25-mg Captopril test (CAP) on doxazosine and/or long-acting verapamil, positive for PHA if aldosterone ≥ 130 pg/ml or ARR ≥ 50, 1 or 2 h post-captopril. Patients negative for PHA with basal CAP ARR ≥ 50 or low renin levels were diagnosed with AAH. MRB (50–100 mg spironolactone or 200–300 mg eplerenone) as sole BP medication. BP (mmHg). Mann–Whitney *U*, Student's *t*, and Wilcoxon, χ^2 tests. SPSS 15.
Results
Baseline characteristics HAP vs AAH: 28/60 vs 32/60 patients, 67.9% vs 75% women, mean age 55.4 (S.D.: 2.7) vs 53.9 (S.D.: 9.9). Number BP-lowering drugs: 2 (IQR: 1–2) vs 1 (IQR: 1–2). Resistant hypertension (RH): 6/28 (21.4%) vs 2/32 (6.3%). Major CV events and/or renal failure: 8/28 (28.6%) vs 5/32 (15.6%), $P=0.06$. Hypokalemia: 5/28 (17.8%) vs 0/32 (0%), $P=0.003$. Serum potassium (mmol/l) (SK): 4.0 mmol/l (S.D.: 0.6) vs 4.2 (S.D.: 0.5) (*n*: 3.5–5.5), serum creatinine (mg/dl) (SC): 1.0 (S.D.: 0.5) vs 0.89 (S.D.: 0.3), office systolic BP (SBP): 154 (S.D.: 22.6) vs 151 (S.D.: 16.6), office diastolic BP (DBP): 90 (S.D.: 14.4) vs 90 (S.D.: 12.1). Response to 2 weeks of MRB: SBP 128 (S.D.: 15.7) vs 123 (S.D.: 11.8), DBP: 77 (S.D.: 10.7) vs 75 (S.D.: 9.1). SK: 4.6 (S.D.: 0.5) vs 4.7 (S.D.: 0.5). SC: 1.14 (S.D.: 0.7) vs 1.00 (S.D.: 0.4). The descent in both SBP and DBP was significant in PHA (both $P<0.001$) as in AAH (both $P<0.001$). No significant differences were found in SBP ($P=0.569$) nor DBP ($P=0.389$) reductions following MRB in PHA vs AAH.
Conclusion
The CAP can identify both patients with PHA and AAH. Both groups present a similar, dramatic and rapid BP response to high-dose MRB, suggesting that AAH patients should be identified, and the same protocol for medical therapy used in PHA and AAH. Furthermore, our results support the hypothesis that aldosterone-induced hypertension is a continuum.

DOI: 10.1530/endoabs.37.GP.03.05

GP.03.06

Applying a new decision threshold to an old test: does the measurement of plasma metanephrines in patients fasting and supine improve diagnostic sensitivity?

Ruth Casey, Marcia Bell, Michael Dennedy & Paula O'Shea
Galway University Hospital, Galway, Ireland.

The recently published Endocrine Society Clinical Practice guideline on phaeochomocytoma and paraganglioma (PPGL) recommends measuring plasma metanephrines (PMets) with patients in the supine position after an overnight fast and using appropriately defined reference intervals.[1] Studies have shown higher diagnostic sensitivities using the latter pretesting criteria.[2] However, this testing protocol is resource intensive and arguably impractical in routine clinical practice. In our institution blood samples for PMets are collected with patients non-fasting and seated using reference intervals established accordingly. The aim of the present study was to assess the effects on diagnostic test performance retrospectively in patients who underwent PMets screening in our institution between 2009 and 2014 using reference intervals derived in subjects fasting and supine. A total of 150 patients were included in this study. There were 79 males (53%) and 71 females (47%). The mean age was 54.3 years (S.D. 6 years). A total of 45 (30%) patients would have had a positive test result based on the supine reference interval being applied vs a total of 8 (5.3%) patients who screened positive using the decision thresholds derived in seated subjects. There were 6 (4%) patients with histologically confirmed PPGL in this cohort and no case would have been missed using the non-fasting and seated reference intervals for PMets. The most common alternative diagnosis for the 39 patients who screened positive for PMets using the new supine reference interval but who did not have a diagnosis of PPGL was essential hypertension ($n=19$, 48.7%). This study demonstrates that the existing, more pragmatic pretesting protocol for PMets collection resulted in no false-negative biochemical screening for PMets over a 5-year period and that application of a supine reference interval would have resulted in 39 false-positive results in this same time period.
References
1. *J Clin Endocrinol Metab* 2014 **99** (6) 1915–1942.
2. *Clin Endocrinol (Oxf)* 2014 **80** (4) 478–486.

DOI: 10.1530/endoabs.37.GP.03.06

GP.03.07

Comparison of urinary metanephrine concentrations after unilateral adrenalectomy for pheochromocytoma to healthy subjects

Yoon Young Cho, Dong Ik Cha, Jae Hoon Chung, Sun Wook Kim & Jae Hyeon Kim
Samsung Medical Center, Seoul, Republic of Korea.

Background
Urinary metanephrine (MN) and normetanephrine (NMN) are used to detect recurrence of pheochromocytoma during post-operative period. Currently, reference ranges of urinary MN and NMN obtained from healthy individuals are applied to subjects with adrenalectomy. However, studies regarding the property of using reference ranges from healthy subjects in pheochromocytoma subjects with adrenalectomy are limited.
Aim
To compare urinary MN and NMN concentrations in patients after unilateral adrenalectomy to concentrations in healthy subjects.
Methods
A single-center retrospective study was conducted in pheochromocytoma patients confirmed with pathology. Eighty-two patients underwent unilateral adrenalectomy between February 2004 and June 2014 and had no evidence of recurrence during follow-up period. Urinary MN and NMN were checked before and after surgery with 3- or 6 month-intervals.
Results
Urinary MN concentration after unilateral adrenalectomy was lower than control group (70.0 μg/day vs 92.0 μg/day, $P<0.001$), whereas urinary NMN was not

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

Conclusions

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

DOI: 10.1530/endoabs.37.GP.03.07

GP.03.08

Obstructive sleep apnea presenting as pseudophaeochromocytoma

Hela Marmouch[1,2], Sondes Arfa[1], Tasnim Slim[1], Fadia Boubaker[1], Manel Jmal[1,2], Hanene Sayadi[1,2] & Ines Khochtali[1,2]
[1]Department of Internal Medicine–Endocrinology, Monastir, Tunisia; [2]Faculty of Medicine, Monastir, Tunisia.

Introduction

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

Case report

A 52-year-old female with a history of poorly controlled resistant HTA was admitted to our hospital with severe HTA. She had a history of fatigue and intermittent episodes of palpitations. Laboratory evaluation was significant for elevated 24-h urinary catecholamine levels (CU=3.5×). This case was presenting with a clinical and biochemical picture indistinguishable from that of phaeochromocytoma. However, neither computed tomography nor MIBG scintigraphy detected any catecholamine-producing tumor in or outside the adrenal glands. Our patient was screened with full polysomnography because of heavy snoring, daytime somnolence, and obesity. It revealed severe (OSAS). After three months of continuous positive airway pressure therapy, the patient experienced resolution of his presenting symptoms, improved blood pressure control and normalisation of his CU. This case highlights sleep disordered breathing as a potentially reversible cause of pseudo phaeochromocytoma (PPH).

Discussion

The OSAS can elevate catecholamine secretion and increased sympathetic activity which may mimic the biochemical profile of PPH. Treatment of OSAS may normalise the effects of this sympathetic overdrive and resolve excessive CU secretion. In this observation, we report a case of PPH caused by OSAS; a common medical condition which is less recognised as a cause of raised catecholamines.

DOI: 10.1530/endoabs.37.GP.03.08

Steroids

GP.04.01

Dual 5α-reductase inhibition causes hepatic lipid accumulation in man

Jonathan Hazlehurst[1], Andrei Oprescu[2], Nikolaos Nikolaou[1], Annabel Grinbergs[3], Nigel Davies[4], Robert Flintham[4], Beverley Hughes[2], Angela Taylor[2], Jinglei Yu[5], Anton Wagenmakers[5] & Jeremy Tomlinson[1]
[1]OCDEM, University of Oxford, Oxford, UK; [2]CEDAM, University of Birmingham, Birmingham, UK; [3]NIHR/Wellcome Trust Research Facility, University Hospitals Birmingham, Birmingham, UK; [4]MRI Physics, University Hospitals Birmingham, Birmingham, UK; [5]School of Sport and Exercise Science, University of Birmingham, Birmingham, UK.

5α reductases 1 and 2 (SRD5A1 and SRD5A2) metabolise cortisol into inactive 5α-dihydrocortisol contributing to the regulation of cortisol availability in addition to their established role in the generation of dihydrotestosterone from testosterone. Dutasteride and finasteride are commonly prescribed to patients with benign prostatic hyperplasia but their potential metabolic effects have only recently been identified. Dutasteride inhibits both SRD5A1and SRD5A2 whilst finasteride inhibits SRD5A2 alone. Importantly, mice with deletion of SRD5A1 are more susceptible to hepatic steatosis and fibrosis. We conducted a randomised, double-blind study in 12 healthy male volunteers (age 36.3±4.4 years, BMI (kg/m^2) 26.6±1.2). Volunteers underwent hepatic magnetic resonance spectroscopy to evaluate intrahepatic lipid content and a series of detailed metabolic assessments including adipose microdialysis and a hyperinsulinaemic–euglycaemic clamp incorporating stable isotopes to measure lipogenesis and glucose handling. Subjects were then randomised to receive either finasteride (5 mg OD) or dutasteride (0.5 mg OD) for 21 days then all investigations were repeated. Dutasteride, not finasteride increased hepatic glucose output (EGP (mg/kg per min) D: 0.609±0.07, 0.924±0.14, $P=0.046$; F: 0.711±0.12, 0.539±0.08, $P=0.19$). Neither, impacted peripheral glucose disposal. Adipose tissue interstitial release of glycerol was decreased by dutasteride in the presence of insulin (AUC glycerol (μmol/l) D: 203±30.6, 104.5±22.1, $P=0.01$; F: 151.02±36.9, 160.7±21.7, $P=0.83$). Although, dutasteride increased de novo lipogenesis, this did not reach statistical significance. (D: 1.21±0.36, 6.50±2.7%, $P=0.14$; F: 1.55±0.51, 1.33±0.33%, $P=0.64$). Intrahepatic lipid increased after dutasteride, but not finasteride treatment (PDFF%: D: 0.88±0.49, 1.15±0.57, $P=0.04$; F: 3.05±2.24, 3.69±2.84, $P=0.36$). Furthermore, there was a positive correlation between change in DNL and change in hepatic steatosis in those treated with dutasteride (R^2, $P<0.01$). In conclusion, inhibiting SRD5A1 with dutasteride promotes an adverse metabolic phenotype resulting in increased intrahepatic lipid and endorses previous observations in rodent studies. Further detailed studies are needed in patients prescribed 5α-reductase inhibitor therapy.

Disclosure

This work was supported by the Medical Research Council (Senior Clinical Fellowship G0802765, to J Tomlinson). Additional equipment was provided through Advantage West Midlands Science City.

DOI: 10.1530/endoabs.37.GP.04.01

GP.04.02

The modulation of corticosteroid metabolism by hydrocortisone therapy in patients with hypopituitarism increases tissue glucocorticoid exposure

Mark Sherlock[1,2,3], Lucy Ann Behan[4], Mark Hannon[4], Aurora Aragon Alonso[1], Christopher Thompson[4], Robert Murray[5], Nicola Crabtree[6], Beverly Hughes[1], Wiebke Arlt[1], Amar Agha[4], Andrew Toogood[1] & Paul M Stewart[1]
[1]Centre for Endocrinology, Diabetes and Metabolism, University of Birmingham, Birmingham, UK; [2]Department of Endocrinology and Diabetes, Adelaide and Meath Hospitals, Incorporating the National Children's Hospital, Dublin, Ireland; [3]Trinity College Dublin, Dublin, Ireland; [4]Department of Endocrinology, Diabetes and Metabolism, Beaumont Hospital and RCSI Medical School, Dublin, Ireland; [5]Department of Endocrinology, Leeds Teaching Hospitals NHS Trust, St James's University Hospital, Leeds, UK; [6]Department of Nuclear Medicine, Queen Elizabeth Hospital, Birmingham, UK.

Context

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

Objective

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

Design and patients

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

Setting

Endocrine Centres within University Teaching Hospitals in UK and Ireland.

Main outcome measures

Urinary corticosteroid metabolite profile and body composition assessment.

Results

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

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

DOI: 10.1530/endoabs.37.GP.04.02

GP.04.03

Using a morning cortisol to predict adrenal reserve and guide management

Conor Woods[1], Nicola Argese[3], Matthew Chapman[2], Rachel Webster[4], Andrew Toogood[2], Wiebke Arlt[2], Paul Stewart[5], Rachel Crowley[2] & Jeremy Tomlinson[1]
[1]Oxford Centre for Diabetes Endocrinology and Metabolism, University of Oxford, Oxford, UK; [2]Centre for Endocrinology, Diabetes and Metabolism, University of Birmingham, Birmingham, UK; [3]Department of Endocrinology, St Andrea Hospital, Rome, Italy; [4]Department of Biochemistry, Queen Elizabeth Hospital, University of Birmingham, Birmingham, UK; [5]Department of Endocrinology, University of Leeds, Leeds, UK.

Background
The short Synacthen test (SST) is the most widely used dynamic assessment of adrenal reserve. In some situations, the SST may be difficult to perform. Random basal cortisol levels could provide an alternative screening assessment to rationalize which patients need dynamic testing. This is highly clinically relevant, given the large numbers of patients taking prescribed glucocorticoids who are at risk of iatrogenic adrenal suppression.
Methods
3603 SST results (all performed in the morning) were analysed from electronic records in a large secondary/tertiary centre across all specialities. A 30 min cortisol value >549 nmol/l was defined as a pass. Results were divided into subgroups including age, sex, pituitary, and adrenal pathology and patients taking inhaled corticosteroids (ICS). Receiver operator characteristic curves were used to generate area under the curve (AUC), best-fit cortisol values and to predict cut-off values for specificities and sensitivities.
Results
Baseline and 30 min cortisol levels correlate positively ($r=+0.74$, $P<0.0001$). Basal cortisol levels >440 and ≥506 nmol/l gave 99 and 100% specificity respectively for passing the SST. Baseline cortisol <107 nmol/L gave a 99% sensitivity for failing. Cut-off values and AUCs were similar between groups divided by sex, age, and menopausal status. In patients currently taking ICS, 31% failed an SST (71/226). Patients taking ICS with a basal cortisol ≥359 nmol/l (36%, $n=81$) passed, and those with a cortisol <34 nmol/l (4%, $n=9$) failed an SST. In post-pituitary surgery patients ($n=329$), those with basal cortisol above 350 nmol/l (23%) passed, and those below 46 nmol/l (11%) failed the SST.
Conclusion
Baseline cortisol levels can be informative in predicting the SST response. A high clinical index of suspicion of adrenal insufficiency mandates dynamic assessment of adrenal reserve by SST. However, a basal cortisol may have a clinical utility in discrete patient cohorts, such as those on ICS, in whom, within our cohort, 40% ($n=90$) of SSTs could have been avoided.
Disclosure
This work has been supported by the Medical Research Council (Senior Clinical Fellowship ref. G0802765, J Tomlinson).

DOI: 10.1530/endoabs.37.GP.04.03

GP.04.04

Regulation of lipogenesis in human hepatocytes by androgens, glucocorticoids, and 5α-reductase

Nikolaos Nikolaou[1,3], Maryam Nasiri[2], Sylvia Parajes[2], Nils Krone[2], George Mastorakos[3], George Valsamakis[3], Beverly Hughes[2], Angela Taylor[2], Iwona Bujalska[2], Laura Gathercole[1] & Jeremy Tomlinson[1]
[1]University of Oxford, Oxford, UK; [2]University of Birmingham, Birmingham, UK; [3]University of Athens, Athens, Greece.

Non-alcoholic fatty liver disease (NAFLD) is rapidly becoming the commonest cause of liver cirrhosis and leading indication for liver transplant worldwide. It is tightly associated with obesity and type 2 diabetes, yet the precise mechanisms that drive its aetiology are not fully defined. Dysregulation of both glucocorticoid and androgen metabolism has been implicated in its pathogenesis. The availability of these hormones to bind and activate their receptors is mainly regulated by 5α-reductase type 2 (5αR2) that inactivates glucocorticoids and converts testosterone to dihydrotestosterone (DHT). We have therefore explored the role of androgens and glucocorticoids and their metabolism by 5αR2 upon lipid homeostasis in human hepatocytes. In human hepatoma cell lines, androgen treatment (testosterone and DHT) increased *de novo* lipogenesis (DNL) (7001.8±258.58 (ctrl) vs 8747.76±433.39 (testosterone) and 8970.03±330.17 (DHT), $P<0.05$). Furthermore, androgen receptor (AR) over expression, even in the absence of androgens, increased lipogenesis (7001.8±258.58 (ctrl) vs 14 193.2±755.17 (AR), $P<0.05$). Changes in lipid accumulation were paralleled by changes in lipogenic gene expression including fatty acid synthase (FASN) and acetyl CoA carboxylase (ACC1) (FASN: ctrl 13.90±1.99 vs AR 66.78±6.22 and ACC1: ctrl 1.06±0.26 vs AR 3.52±0.29, $P<0.05$). Similar observations were made in primary human hepatocytes from female, but not male donors. Glucocorticoids decreased DNL, an effect that was abrogated by over expression of 5αR2 and augmented by pharmacological inhibition of 5αR2 activity. In conclusion, we have demonstrated the ability of androgens and glucocorticoids to regulate lipogenesis in human hepatocytes. In addition, we have identified the potential for ligand independent activation of the androgen receptor to alter lipid flux. Finally, modulation of 5αR2 activity has the ability to regulate local steroid hormone availability that can impact upon metabolic phenotype within hepatocytes that may have implications for those patients currently taking 5αR inhibitors.
Disclosure
This work was supported by the Medical Research Council (MRC) (grant number G0802765).

DOI: 10.1530/endoabs.37.GP.04.04

GP.04.05

Glucocorticoid receptor and HSD11B1 gene polymorphisms influence the therapy and therapy-associated morbidities in patients with Addison's disease

Agnes Molnar[1], Annamaria Kovesdi[1], Nikolette Szucs[1], Miklos Toth[1], Peter Igaz[1], Karoly Racz[1,3] & Attila Patocs[2,4]
[1]2nd Department of Internal Medicine, Semmelweis University, Budapest, Hungary; [2]Lendület' Hereditary Endocrine Tumours Research Group, Budapest, Hungary; [3]Molecular Medicine Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest, Hungary; [4]Department of Laboratory Medicine, Semmelweis University, Budapest, Hungary.

Objective
Glucocorticoids exert their effects through the glucocorticoid receptor (GR). The local, cell-type specific glucocorticoid effect is modulated by the 11β-hydroxysteroid dehydrogenase enzymes (HSD11B) responsible for the interconversion of cortisone and cortisol. Individual sensitivity against glucocorticoids and activity of the HSD11B enzymes are at least partly determined by genetic factors.
Aim
To test whether SNPs of GR and HSD11B1 genes (N363S-rs6195, BclI-rs41423247, A3669G-rs6198 of GR; and rs12086634, rs4844880 of HSD11B1) influence the glucocorticoid replacement dosage, and clinical/laboratory parameters in patients with Addison's disease.
Patients and methods
67 patients with primary adrenal insufficiency diagnosed and treated at the 2nd Department of Medicine, Semmelweis University were studied. Clinical, laboratory data, and the dosage of the hormone replacement therapy were collected. Peripheral blood DNA was isolated, and the *GR* gene SNPs were examined using allele-specific PCR (for BclI and N363S) or TaqMan assay on real-time PCR (for A3669G, rs12086634, and rs4844880). Genotype distribution was compared to those observed in the general Hungarian population using χ^2 or Fischer' exact *t*-test. ANOVA followed by power analysis was used for association studies.
Results
The allele frequency of *N363S* polymorphism was higher in patients compared to the control group. Among *GR* gene SNPs only the *Bcl1* polymorphism associated with BMI; the number of homozygous carriers was significantly higher than that of heterozygous carriers or non-carriers ($P=0.007$, power: 100%). The disease appeared significantly earlier in patients harboring *A3669G* SNP. The *rs4844880* SNP associated with higher BMI and with higher bodyweight-adjusted glucocorticoid substitution dose, the disease developed in significantly later age in these patients. Annual decrease of bone mineral density, *t*-score and *z*-score at lumbal spine was significantly lower in carriers compared to non-carriers.
Conclusion
SNPs of *GR* and *HSD11B1* genes may be important genetic factors in the pathogenesis and therapy-related morbidities in patients with primary adrenal insufficiency.

Disclosure
The authors acknowledge the financial support from Hungarian Scientific Research Fund (OTKA, PD100648 (A Patocs)) and Technology Innovation Fund, National Developmental Agency (KTIA-AIK-2012-12-1-0010).
DOI: 10.1530/endoabs.37.GP.04.05

GP.04.06

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

Rahel M Büttler[1], Esra Bagci[1], Henk Brand[2], Marinus A Blankenstein[1] & Annemieke C Heijboer[1]
[1]Endocrine Laboratory, Department of Clinical Chemistry, VU University Medical Center, Amsterdam, The Netherlands; [2]Departments of Periodontology and Oral Biochemistry, Academic Centre for Dentistry Amsterdam (ACTA), Amsterdam, The Netherlands.

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

DOI: 10.1530/endoabs.37.GP.04.06

GP.04.07

Differential regulation of 11β-hydroxysteroid dehydrogenase type 1 activity in patients with differing aetiologies of hypopituitarism

Lucy Ann Behan[1], Bairbre Rogers[1], K Maher[2], Norman F Taylor[3], Diarmuid Smith[1], Chris J Thompson[1], John P Monson[2] & Amar Agha[1]
[1]Department of Endocrinology, Beaumont Hospital and RCSI Medical School, Dublin, Ireland; [2]Department of Endocrinology and Chemical Pathology, St Bartholomew's Hospital, London, UK; [3]Department of Endocrinology and Chemical Pathology, King's College Hospital, London, UK.

Pituitary patients with different aetiologies of hypopituitarism exhibit differing phenotypes despite optimal replacement therapy. We hypothesised that differential regulation of the isoenzyme 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1), which mediates the autocrine conversion of cortisone to cortisol in adipose tissues and liver may play a role.
We prospectively studied 11β-HSD1 activity through analysis of 24 h urine cortisol/cortisone metabolites ratio (Table 1). 36 hypopituitary patients with craniopharyngioma, treated remitted Cushing's disease and non-functioning pituitary adenomas or prolactinomas (NFPA or PRL) were studied, on and off GH replacement.
11β-HSD1 activity was higher in subjects with craniopharyngioma both on and off GH evidenced by increased tetrahydrocortisol to tetrahydrocortisone metabolite (THF + 5alloTHF/THE) ratio compared to other diagnostic groups (Table 1). There was no difference in BMI, insulin levels, serum hormone measurements, or hydrocortisone dose between groups.

Table 1

	Craniopharyngioma ($n=9$)	Treated Cushing's disease (n = 8)	NFPA or PRL ($n=19$)
THF + 5alloTHF/THE On GH	1.23 (0.8–1.4)	0.97 (0.44–1.1)	0.73 (0.61–1.04)*
THF + 5alloTHF/THE Off GH	1.3 (0.9–1.4)	0.94 (0.49–1.08)*	0.79 (0.66–1.09)†

Data are median (interquartile range), *$P<0.05$ and †$P<0.01$ are compared to craniopharyngioma.

Craniopharyngioma is associated with altered enhanced 11β-HSD1 activity compared to other diagnostic groups and this may contribute to the altered body composition seen in this condition.
Disclosure
This work was supported by an unrestricted educational grant from Novo Nordisk Ireland.
DOI: 10.1530/endoabs.37.GP.04.07

GP.04.08

Circadian variation in serum cortisol during hydrocortisone replacement is not attributable to changes in cortisol-binding globulin

Kirun Gunganah, John Monson, William Drake & Teng Teng Chung
St Bartholomew's Hospital, London, UK.

Background
Patients taking hydrocortisone replacement for primary or secondary adrenal failure require individual adjustment of their dose. Previous observations in our department suggest that total serum cortisol levels achieved following an afternoon or evening dose of 5 mg hydrocortisone are almost as high as those that result from a 10 mg dose in the early morning; and that the 'area under the cortisol curve' (AUC) generated by an evening 5 mg dose is broader than after 10 mg taken early in the morning. One potential explanation for this phenomenon might be a circadian variation in serum CBG concentration, which may, in turn, impact on the interpretation of cortisol profiles and individual dose selection for patients on hydrocortisone replacement therapy. The purpose of this study was to investigate the hypothesis that there is a circadian variation in CBG levels.
Method and results
A total of 34 male patients divided into three groups (ten patients with non-somatotroph structural pituitary disease on HC replacement, 11 patients with treated acromegaly on HC replacement, and 13 patients with treated acromegaly not on HC replacement) and ten healthy volunteers were included. Cortisol and CBG levels were measured at six time points (0800, 1100, 1300, 1500, 1700, and 1900 h). No significant circadian variation in CBG concentration was found in any of the four groups.
Conclusion
Circadian variation in serum cortisol during hydrocortisone replacement is not attributable to changes in cortisol-binding globulin. Alternatively, such changes in serum cortisol may be explained by other factors including 11β-hydroxysteroid dehydrogenase type 1 activity or circadian changes in the binding capacity of CBG.
Disclosure
This study was supported by an unrestricted investigator-initiated grant from Pfizer, Inc.
DOI: 10.1530/endoabs.37.GP.04.08

GP.04.09

The influence of short-term and prolonged glucocorticosteroid therapy of immunoinflammatory diseases on carbohydrate metabolism

Farida Valeeva & Guzel Nurullina
Kazan State Medical University, Kazan, Russia.

Introduction
The duration and doses of glucocorticoids (GC) are significant prognostic factors of carbohydrate metabolism disturbance (CMD).

Description of methods
165 patients with systemic lupus erythematosus (32.1% patients), systemic vasculitis (27.3% patients), and chronic glomerulonephritis (40.6% patients) were included. 98 patients received GC pulse-therapy (GCPT) (first group), which included i.v. infusion of prednisolone 10–15 mg/kg per day with 250 ml of 0.9% NaCl solution, on 3 consecutive days; course dose was 1800–3000 mg; 67 patients (second group) received oral GC therapy 15–30 mg/day. All patients passed an oral glucose tolerance test (OGTT) after the course of GCPT in the first group and after 5 days of hospital stay in the second group. An evaluation of CMD was performed.
Results
The study revealed that the incidence of CMD depends on the mode of GC therapy and does not depend on the type of immunoinflammatory disease. CMD was more prevalent in patients receiving oral GC therapy. CMD was observed in 33 (33.7%) patients, receiving GCPT and in 54 (80.6%) patients, receiving oral GC ($P=0.035$). Impaired fasting glucose (IFG) (>7.8 mmol/l 2 h after OGTT, high fasting glucose at baseline 5.5–6.1 mmol/l) was found with similar incidence in first and second groups (8 (8.2%) and 14 (20.9%), respectively, $P=0.069$). Impaired glucose tolerance (7.8–11.1 mmol/l 2 h after OGTT) and diabetes mellitus (≥ 11.1 mmol/l 2 h after OGTT) were more prevalent in the second group – in 21 (31.3%) and 19 (28.4%) patients, compared to 13 (13.3%) and 12 (12.2%) patients in the first group respectively ($P=0.038$ and $P=0.049$).
Conclusions
CMD develop more often in patients with immunoinflammatory diseases receiving long-term oral GC therapy, compared to patients on GCPT. All patients should be regularly screened for CMD and receive necessary correction.

DOI: 10.1530/endoabs.37.GP.04.09

Developmental and paediatric endocrinology

GP.05.01

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

Ryan Paul[1,2], Chris McMahon[2], Marianne Elston[1] & John Conaglen[1]
[1]Department of Medicine, Waikato Clinical School, University of Auckland, Hamilton, New Zealand; [2]AgResearch, Ruakura, New Zealand.

The predominant positive and negative regulators of skeletal muscle mass are IGF1 and myostatin respectively. The regulation of skeletal muscle mass, IGF1 and myostatin by the gonadal steroids testosterone and 17β-oestradiol (E_2) remains controversial. Male and female C57BL/6 mice underwent bilateral gonadectomy or sham surgery at 4 weeks of age, with insertion of s.c. silastic implants containing testosterone, E_2, or cholesterol (placebo) ($n=8$/treatment and sex). Blood and hindlimb muscles were collected at 13 weeks of age and muscle mass was normalised to bone length. Concentrations of IGF1 in plasma were determined by ELISA. C2C12 myoblasts were treated under differentiating conditions with testosterone (30 nM) or E_2 (10 nM) for 24 h and RNA was harvested for quantitative PCR. Myoblasts were also treated for 96 h and differentiation was assessed by immunocytochemistry. Sexual dimorphism of normalised hindlimb muscle mass was lost post-gonadectomy. In male mice, gonadectomy reduced normalised hindlimb muscle mass, reduced IGF1 mRNA expression and increased mature myostatin protein abundance ($P<0.001$). Replacement of testosterone normalised these parameters, while replacement of E_2 only normalised hindlimb muscle mass. Concentrations of IGF1 in plasma were not altered by any treatment in males. In female mice, gonadectomy $\pm E_2$ replacement did not alter normalised hindlimb muscle mass or mature myostatin protein abundance, despite reducing concentrations of IGF1 in plasma and skeletal muscle ($P<0.05$). Testosterone significantly increased normalised hindlimb muscle mass, increased concentrations of IGF1 in plasma and skeletal muscle, while reducing the abundance of mature myostatin. Testosterone significantly increased myotube hypertrophy (151%) to a greater extent than E_2 (61%); although, neither altered IGF1 mRNA expression. We conclude that the anabolic action of testosterone on skeletal muscle is partially through modulation of IGF1 and myostatin activity. However, E_2 appears to increase skeletal muscle mass independently of IGF1 or myostatin.
Disclosure
Waikato Medical Research Foundation (grant number 223).

DOI: 10.1530/endoabs.37.GP.05.01

GP.05.02

The differential impact of PAPS synthase isoforms on DHEAS may be explained by an isoform-specific interaction of SULT2A1 with PAPSS2, but not PAPSS1

Jon W Mueller[1], Jan Idkowiak[1], Rebecca E Hardman[1], Philip J House[1], Joanne C McNelis[1], Ian T Rose[1], Vivek Dhir[1], Edina Rosta[2] & Wiebke Arlt[1]
[1]CEDAM, University of Birmingham, Birmingham, UK; [2]Department of Chemistry, King's College London, London, UK.

Human sulfation depends on provision of the universal sulfate donor PAPS by the two PAPS synthase isoforms PAPSS1 and PAPSS2. Mutations in PAPSS2 have been identified as a monogenic cause of androgen excess presenting with premature adrenarche and polycystic ovary syndrome, due to decreased sulfation of the androgen precursor DHEA by DHEA sulfotransferase (SULT2A1) and hence increased conversion of DHEA to active androgens (*New Eng J Med* 2009 **360** (22) 2310–2318 and *J Clin Endocrinol Metab* 2015 jc20143556). Here, we examined why ubiquitously expressed PAPSS1 cannot compensate for the impact of PAPSS2 deficiency on DHEAS. First, we carried out siRNA-mediated knockdown of PAPSS1/2 in the adrenal cell line NCI-H295R1. Real-time PCR confirmed $>90\%$ knockdown and the impact at protein level was assessed by western blot and SULT2A1 activity assays. Efficient knockdown of PAPSS2 reduced DHEAS to $30\pm5\%$. Strikingly, PAPSS1 knockdown did not impact on DHEAS, providing *in vitro* evidence for non-overlapping functionality of the two PAPSS isoforms. To test whether subcellular localisation impacts on isoform-specific capacity to support DHEAS, we used HEK293 cells to co-express SULT2A1 with either WT PAPSS1/2 or exclusively nuclear or cytoplasmic PAPSS1/2 variants. WT and nuclear PAPSS1/S2 equally supported DHEAS; however, SULT2A1 activity with exclusively cytoplasmic expression of PAPSS2 was 1.6-fold higher than with cytoplasmic PAPSS1; suggesting an isoform-specific protein-protein interaction of SULT2A1 with PAPSS2, but not PAPSS1. To examine this further, we carried out docking studies using ClusPro, Z-dock and gramm-X servers employing the APS kinase protein structures 2ofx and 2ax4 for PAPSS1/2 and three different structures for human SULT2A1 (1efh, 3f3y, and 4ifb). Docking of SULT2A1 to PAPSS2 unanimously resulted in more homogeneous complexes than for SULT2A1–PAPSS1, yielding significantly higher scores by the associated docking algorithms. Such an isoform-specific interaction with SULT2A1 may be the underlying mechanism explaining why PAPSS2 deficiency results in disruption of DHEAS despite ubiquitous expression of PAPSS1. Follow-up studies to prove direct interaction of PAPSS2 and SULT2A1, employing pulldown assays and FRET analyses, are currently underway.
Disclosure
Marie Curie IEF award 625451 SUPA-HD (to J W Mueller) and Wellcome Trust project grant 092283 (to W Arlt).

DOI: 10.1530/endoabs.37.GP.05.02

GP.05.03

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

Maria Tsachaki, Julia Birk & Alex Odermatt
University of Basel, Basel, Switzerland.

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

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

Disclosure
Swiss National Foundation.
DOI: 10.1530/endoabs.37.GP.05.03

GP.05.04

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

Matthias K Auer[1], Tao Xu[2], Yasmin Roepke[1], Günter K Stalla[1], Mareike Stieg[1], Eva Van Caenegem[4], Cornelia Prehn[3], Rui Wang-Sattler[2], Jerzy Adamski[3] & Guy T'sjoen[4]
[1]Endocrinology, Diabetology and Internal Medicine, Max Planck Institute of Psychiatry, Munich, Germany; [2]Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, Neuherberg, Germany; [3]Institute of Experimental Genetics, Genome Analysis Center, German Center for Diabetes Research, Neuherberg, Germany; [4]Department of Endocrinology, Ghent University Hospital, Ghent, Belgium.

Introduction
Sex steroid hormones exert a wide range of effects on metabolism. New techniques such as metabolomic profiling allow for a deeper insight into metabolic regulation. In epidemiological samples it has been demonstrated that most of these metabolites show sex-specific differences. However, if these differences are attributable to the effects of sex hormones or genetics is little understood so far.
Methods
We performed targeted metabolomics profiling in serum of fasting transmen (F2M) and transwomen (M2F) at baseline and following 12 months of cross-sex hormone treatment ($n=20$/group). Subjects investigated in this study were part of the European Network for the Investigation of Gender Incongruence (ENIGI). The targeted metabolomics approach was based on ESI–LC–MS/MS measurements by AbsoluteIDQTM p180 Kit (Biocrates Life Sciences AG).
Results
Several metabolites concentrations changed significantly between the two visits in the M2F group including DL-carnitine, octadecanyl-L-carnithine, threonine, alpha-amino adipic acid, hydroxyproline, phosphatidylcholine diacyl C34:3, ornithine, citrulline, and ornithine/arginine ratio (FDR <0.05, $P<0.05$). In the F2M group there was only a significant change in ornithine. After adjustment for age, lifestyle factors and body composition in a linear mixed effects model, these results remained significant but vanished after adjusting for sex hormone levels. This indicates a direct effect of sex hormones on metabolite levels. Opposite effects were seen, i.e. for changes in ornithine levels between the two groups. Ornithine was further strongly positively related to testosterone levels in both groups. These findings are also in line with the sex-specific dimorphism for metabolites observed in epidemiological studies.
Conclusion
In this first pilot study we could show that cross-sex hormone treatment induces several changes in serum metabolites. Our findings indicate a direct effect of sex hormones on different metabolic cycles including lipid metabolism, nitric oxide formation, and amino acid regulation.

DOI: 10.1530/endoabs.37.GP.05.04

GP.05.05

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

Ruta Kriksciuniene[1,2], Birute Zilaitiene[1,2], Rima Berontiene[1,2], Ruta Nakaite[2], Jurate Drazdauskaite[2] & Rasa Verkauskiene[1,2]
[1]Hospital of Lithuanian University of Health Sciences Kauno Klinikos, Kaunas, Lithuania; [2]Lithuanian University of Health Sciences, Kaunas, Lithuania.

Aim
To compare final height and late metabolic outcomes depending on oestrogen replacement initiation in Turner syndrome (TS).
Subjects
Women with TS ≥ 18 years retrospectively treated with GH and oestrogen.
Methods
Records of 117 women with TS from database of Hospital of Lithuanian University of Health Sciences were analysed. 71 did not matched the inclusion criteria; 46 patients were enrolled and divided into two groups: early oestrogen group (eE) – EI before 15 years ($n=27$, EI at a median of 13 years, range from 13 to 14 years) and delayed oestrogen group (dE) – EI ≥ 15 years ($n=19$, EI at a median of 16 years, range 16–18 years). Final height, height gain, BMI, fasting glucose, blood pressure, and bone density was compared between the groups.
Results
GH treatment was started at a median age of 11 years (range 9–12 years) in the eE and of 15 years (range 9.25–16.75 years) in the dE group ($P=0.005$). The final height was similar in both groups: median of 153 cm (range 148–156 cm) in the eE and 152 cm (range 47–155 cm) in the dE ($P=0.655$). The height before EI in the eE group was -2.26 and -2.90 SDS in dE group ($P=0.055$). Height gain was greater ($P<0.05$) in eE (median 11 cm, range 7.1–15 cm) than in dE (median 5.25 cm, range 2.5–8.1 cm) group. No significant differences in metabolic parameters have been identified between the groups (mean age 27 ± 5.6 years).
Conclusion
Puberty induction at a physiological age does not have negative effect on final height in TS patients, providing earlier start of oestrogen treatment. No relation between oestrogen initiation time and metabolic parameters during later life span had been found.

DOI: 10.1530/endoabs.37.GP.05.05

GP.05.06

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

Rahel M Büttler[1], Frans Martens[1], Flaminia Fanelli[2], Brian G Keevil[3], Hai T Pham[4], Mark M Kushnir[5], Angela E Taylor[6], Tue Soeborg[7], Marinus A Blankenstein[1] & Annemieke C Heijboer[1]
[1]Endocrine Laboratory, Department of Clinical Chemistry, VU University Medical Center, Amsterdam, The Netherlands; [2]Endocrinology Unit, Department of Medical and Surgical Sciences, Center for Applied Biomedical Research, S. Orsola Malpighi Hospital, University of Bologna, Bologna, Italy; [3]Department of Clinical Biochemistry, University Hospital of South Manchester, Manchester, UK; [4]Biocrates Life Sciences AG, Innsbruck, Austria; [5]Department of Pathology, ARUP Institute for Clinical and Experimental Pathology, University of Utah, Salt Lake City, Utah, USA; [6]School of Clinical and Experimental Medicine, Centre for Endocrinology, Diabetes and Metabolism, University of Birmingham, Birmingham, UK; [7]Department of Growth and Reproduction, Faculty of Health and Medical Sciences, Rigshospitalet, Copenhagen University Hospital, University of Copenhagen, Copenhagen, Denmark.

Recently, liquid chromatography–tandem mass spectrometry (LC–MS/MS) was stated to be the method of choice to measure sex steroids.[1] Information on the mutual agreement of LC–MS/MS methods, however, is scarce. Therefore, we compared seven published LC–MS/MS methods for the simultaneous measurement of testosterone, androstenedione, and DHEA. Fifty-five random serum samples obtained from volunteers were analysed in duplicate by seven published LC–MS/MS methods.[2,3,4,5,6,7] We performed a Passing–Bablok regression analysis and calculated a Pearson's correlation coefficient to assess the agreement of the investigated methods with one of the methods in this study, arbitrarily chosen as 'reference method'. Moreover, we calculated the intra-assay coefficient of variation (CV) of each method using the duplicate results. Concentrations of testosterone, androstenedione, and DHEA were 0.2–29, 0.4–5.2, and 1.8–18 nmol/l respectively. The slopes of the regression lines calculated by Passing–Bablok regression analysis ranged from 0.92–1.05 to 1.01–1.15 for testosterone values, for the entire data set and testosterone for concentrations below 2 nmol/l respectively. For androstenedione and DHEA the slopes were 0.96–1.28 and 0.96–1.46 respectively. The correlation coefficients ranged 0.987–0.997, 0.926–0.988, 0.925–0.971, and 0.955–0.988 for all testosterone values, testosterone concentrations below 2 nmol/l, androstenedione, and DHEA respectively. The intra-assay CV were 1.2–6.2, 2.9–10, 2.7–6.9, and 4.3–16% for testosterone values higher than 2 nmol/l, testosterone concentrations below 2 nmol/l, androstenedione, and DHEA respectively. In conclusion, in general the investigated LC–MS/MS methods for simultaneous measurement of testosterone, androstenedione, and DHEA, showed a good agreement. However, there appear to be differences in standardisation between some of the assays and a high variation in some of the assays.
References
1. Handelsman DJ *et al. J Clin Endocrinol Metab* 2013.
2. Büttler RM *et al. Clin Chim Acta* 2014.
3. Fanelli F *et al. Steroids* 2011.
4. Koal T *et al. J Steroid Biochem Biol* 2011.
5. Kushnir MM *et al. Clin Chem* 2010.
6. O'Reilly MW *et al. J Clin Endocrinol Metab* 2014.
7. Soeborg T *et al. Clin Chim Acta* 2013.

DOI: 10.1530/endoabs.37.GP.05.06

GP.05.07

Prediction of affective disorders in adult men on the basis of steroid profiling

Martin Hill[1], Daniela Ripova[2], Pavel Mohr[2], Marta Velikova[1], Marie Bicikova[1], Michaela Duskova[1] & Luboslav Starka[1]
[1]Institute of Endocrinology, Prague, Czech Republic; [2]National Institute of Mental Health, Klecany, Czech Republic.

A number of evidence indicate that mood (affective) disorders are influenced by various bioactive steroids such as corticoids, sex hormones and neuroactive steroids. However, to date, there are limited data concerning the discrimination between patients suffering from the disorders and controls, or regarding the classification of individual subtypes of mood disorders on the basis of steroid profiling. Therefore 47 steroids including their conjugates and further related substances were measured in sera from male volunteers suffering from depressive disorders (D, $n=20$), anxiety disorders (AN, $n=20$), and in the group of age-comparable controls (C, $n=30$) using GC–MS and immunoassays. Based on this data, multivariate models for discrimination of D and C (sensitivity = 100% and specificity = 100%), AN and C (sensitivity = 100% and specificity = 100%), and D and AN (sensitivity = 85% and specificity = 90%) were built. When discriminating pathologies D and AN from C, the relevant predictors progesterone, allopregnanolone, and conjugated steroids negatively correlated with both AN and D groups, while LH showed the positive correlations. In addition, 5α-dihydrotestosterone and pregnanolone negatively correlated with D, while androstenedione, cortisol, 16α-hydroxy-steroids, and SHBG showed the positive correlations. Finally, pregnenolone, 20α-dihydropregnenolone, 7β-hydroxy-DHEA, and 5-androstene-3β,7α/β,17β-triols positively correlated with AN. In model discriminating the D and AN, the relevant predictors progesterone and cortisol positively correlated with AF, while LH, SHBG, sulphated Δ^5 steroids, and 16α-hydroxy-DHEA showed the negative correlations. In conclusion, various circulating steroids including the neuroactive and neuroprotective ones efficiently predicted two groups of affective diseases in adult men. The data indicated suppressed activities of CYP17A1 and SULT2A1 enzymes in adrenal zona reticularis in affective patients and even more in depressive men. In addition, the results pointed to stimulated activities of immunoprotective 16α-hydroxylating- (CYP3A7) and 7β-hydroxylating enzymes (CYP3A4) in D and AN patients respectively.

Disclosure
Supported by grants IGA NT/13890-4 and NT12211-5 from the Czech Ministry of Health.

DOI: 10.1530/endoabs.37.GP.05.07

GP.05.08

A simple and rapid method for steroid profiling by two dimensional liquid chromatography–tandem mass spectrometry: toward routine application

Flaminia Fanelli, Marco Mezzullo, Alessia Fazzini, Matthew Pedercini, Renato Pasquali & Uberto Pagotto
Endocrinology Unit, Department of Medical and Surgical Sciences, Center for Applied Biomedical Research, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy.

Steroid testing has a central role in clinical decision-making and in research studies on diseases such as hypercortisolisms, female hyperandrogenism, male hypogonadism or inborn disorders of steroid synthesis. Recently, liquid chromatography–tandem mass spectrometry (LC–MS/MS) proved its superiority to routine immunoassays (IA) in accurately and sensitively measuring low level steroids. However, the replacement of automated IA with LC–MS/MS platforms is limited by the need for extraction procedures requiring operator handwork, large sample volume and long runtime. Aiming at improving LC–MS/MS practicability, we developed a 2D-LC–MS/MS method for simultaneously determining serum cortisol, testosterone, androstenedione, 17OHprogesterone (OHP), and 17OHpregnenolone (OHp) based on minimal sample preparation. One hundred µl of serum were treated by protein precipitation, diluted with H_2O and injected into the Prominence-LCMS-8050-electrospray ionisation platform (Shimadzu). Sample underwent on-line purification on perfusion column (6 ml/min, 3 min) and separation on Shim-pack XR-ODS-50×3 mm, 2 µm column (Shimadzu) in 5 min H_2O/acetonitrile gradient, before 7 min clean-up and reconditioning program. Total runtime was 15 min. Quantitative and qualitative transitions were monitored for each analyte. Isotopic dilution quantitation was performed by using d4-cortisol, d5-testosterone, d5-androstenedione, d8-OHP, and $13C_3$-estrone as internal standard for cortisol, testosterone, androstenedione, OHP, and OHp respectively. Lower limits of quantitation (pg on column) assessed in calibrators diluted in BSA (4%) were 122.1 pg/ml (1.5 pg), 9.77 pg/ml (0.12 pg), 19.5 pg/ml (0.24 pg), 39.1 pg/ml (0.49 pg), and 312.5 pg/ml (3.9 pg), and functional sensitivity assessed in charcoal-stripped serum was 122.1, 19.5, 19.5, 39.1, and 312.5 pg/ml for cortisol, testosterone, androstenedione, OHP, and OHp respectively, and was stable along 150 samples batch. Intra- and inter-assay CV ranged between 3.4–7.2% and 5.8–16.7% respectively. Androstenedione comparison with an established extractive LC–MS/MS assay revealed optimal correlation (r: 0.9933–0.9996) and slope coefficients (0.810–1.060). These preliminary data showed that our 2D-LC–MS/MS method for five steroids based on minimal sample preparation achieves performance and robustness levels that can definitively reconcile routine need for reliability and practicability.

Disclosure
This work was supported by the Emilia Romagna Region-University Program for Young Investigators 'Alessandro Liberati' 2010–2012 PRUA 1-2012-004.

DOI: 10.1530/endoabs.37.GP.05.08

GP.05.09

Investigation of the effects of aldosterone on the cardiac cycle in the HL-1 mouse atrial cardiomyocyte cell line

Kostantinos Tsirlis[1], Anastasios Tsarouhas[1], Eleni Aggelidou[1], Efstratios Kosmidis[1], Aristeidis Kritis[1], Maria Albani[1] & Konstantinos Kallaras[2]
[1]Laboratory of Physiology, Aristotle University Medical School, Thessaloniki, Greece; [2]Laboratory of Experimental Physiology, Aristotle University Medical School, Thessaloniki, Greece.

Introduction
Aldosterone (Aldo) decreases the rate of repolarization in rabbit cardiomyocytes and significantly increases the duration of the monophasic action potential in patients with supraventricular arrhythmias, few minutes after its intravenous administration, implying for a non-genomic action. We have previously found a positive linear regression between left ventricular systole duration and plasma Aldo levels in NZW rabbits. To investigate the veracity of the above finding on cardiac cycle (CC) phases and elucidate the underlying mechanism we employ the HL-1 cell line of mouse atrial cardiomyocytes.
Materials and methods
Confluent beating HL-1 cells were stained with 68 µM di-8-ANEPS in 68 µM Pluronic F-127. Cell beating and the accompanied fluorescent intensity changes, were recorded with a specialized high frequency sampling (1 kHz) CMOS camera (NeuroCMOS-SM128f, Redshirt Imaging, Inc., USA) coupled to a fluorescent microscope (AxioExaminer Z1, Carl Zeiss Microimaging GmbH, Germany). 15 optical recordings, of 2 s duration, were taken 1 min apart. 50 µM Aldo in Claycomb's medium was added between the third and fourth recording (control received only the same volume of medium). CC total duration, contraction period (corresponding to cardiac systole) as well as relaxation period and duration of the 'quite' state of the cells (both corresponding to cardiac diastole) were calculated.
Results
Our results show that Aldo increases the total duration of the CC ($P<0.001$ (Z-score (standard score) and Spearman's ρ)) almost immediately after its addition to the cells lasting up to 14 min, when recordings were stopped. This increase is attributed to the 'quite' state of the cells corresponding to the diastolic phase of the CC.
Conclusion
Aldo causes a reduction of the beating frequency of the HL-1 cells. Their prompt response to Aldo denotes a non-genomic action. Taking into account of our previous finding, this action can be attributed to elongation of the first part of cardiac diastole (protodiastole).

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

DOI: 10.1530/endoabs.37.GP.05.09

GP.05.10

Ghrelin and GHSR1 receptor in placentas of SGA, LGA, and AGA newborns

Martha I Gonzalez Dominguez[1], Maria Luisa Lazo de la Vega Monrroy[1], Silvio Zaina[1], Myrna Sabanero[2], Leonel Daza-Benítez[3], Juan Manuel Malacara[1] & Gloria Barbosa-Sabanero[1]
[1]Health Sciences Division, Medical Sciences Department, University of Guanajuato, Leon, Guanajuato, Mexico; [2]Natural and Exact Sciences Division, Biology Department, Guanajuato University, Guanajuato, Guanajuato, Mexico; [3]UMAE No. 48 IMSS, Leon, Guanajuato, Mexico.

Introduction
Intrauterine growth is a biological process regulated by maternal, placental, and foetal endocrine signals. Birth weight is an indicator of the health of the newborn. Alterations in foetal growth lead to perinatal health risks and favour metabolic diseases during adult life. Therefore, the study of endocrine factors determining birth weight, such as ghrelin is an important issue. Ghrelin may exist as two molecular forms, desacyl ghrelin (DAG) and acyl ghrelin (AG). Current evidence showed to DAG as an active hormone with effects on different tissues in diverse physiological and pathophysiological states. Although cord blood (CB) ghrelin levels have been correlated to birth weight, it is unknown which ghrelin's molecular variants are involved and if expression and methylation of ghrelin receptor (GHSR1) has a key role in foetal development.
Methods
We performed a cross-sectional comparative study healthy mothers and their term newborns small for gestational age (SGA), adequate for gestational age (AGA), and large for gestational age (LGA) ($n=20$/group). Total ghrelin, AG, and DAG levels were measured in CB by ELISA. Placental GHSR1 expression was evaluated by western blot and GHSR1 promoter methylation by qPCR after bisulphite modification of DNA.
Results
Cord blood DAG levels were increased in SGA compared to AGA newborns (902.1 ± 109.1 and 597.4 ± 58.2 pg/ml, respectively, $P=0.01$) while LGA and AGA showed similar values (627.2 ± 76.4 pg/ml for LGA, $P=0.80$). DAG levels negatively correlated with birth weight ($r=-0.31$, $P=0.02$) and placental weight ($r=-0.33$, $P=0.02$). No differences in AG or total ghrelin levels were found. Expression and methylation of GHSR1 in placenta was not differentially among SGA, AGA, and LGA.
Conclusions
Our results showed that expression and methylation of ghrelin receptor (GHSR1) has unrelated with birth weight. Suggesting that additional factors, such as DAG, are involved in the mechanism that determines birth weight.
Disclosure
This study was supported by University of Guanajuato (0095/13) and FOMIX CONACYT – Guanajuato State Government (GTO-2012-C03-195238). M I Gonzalez Dominguez was the recipient of CONACYT (CVU-217761).
DOI: 10.1530/endoabs.37.GP.05.10

Reproduction: Female and PCOS

GP.06.01

Habitual physical activity is associated with lower prevalence of insulin resistance in women with polycystic ovary syndrome

Fernanda Mario[1,2], Scheila Graff[1,2] & Poli Mara Spritzer[1,2]
[1]Gynecological Endocrinology Unit, Division of Endocrinology, Hospital de Clinicas de Porto Alegre, Porto Alegre, RS, Brazil; [2]Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil.

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting 7–18% of women of reproductive age, according to different criteria. Metabolic disturbances related to PCOS include dyslipidemia, obesity, and insulin resistance (IR) and women with PCOS have higher prevalence of impaired glucose tolerance and type 2 diabetes mellitus in comparison with weight-matched women without the syndrome. Evidence indicates that regular practice of physical activity improves insulin resistance in general population. Habitual physical activity is defined as any form of body movement with energy expenditure above resting levels, including work, leisure activities, and household chores. The aim of this study was to evaluate whether habitual physical activity is associated with less insulin resistance in women with PCOS. One hundred and four participants, 61 PCOS, by the Rotterdam criteria, and 43 control women, were stratified according to physical activity status: inactive (<7500 steps/day) or active (≥ 7500 steps/day). Habitual physical activity was assessed by counting the number of daily steps, using a digital pedometer. Anthropometric, clinical, and laboratory examination were also determined. The age of participants was 23.9 ± 6.4 years old and most of them were Caucasians. While BMI was higher in PCOS than in controls, it was similar between active and inactive participants of each group. Androgen levels and HOMA-IR were higher and sex hormone-binding globulin was lower in PCOS compared to controls ($P<0.05$). Abnormal fasting insulin (≥ 20 μIU/ml) was found to be less frequent in active than in inactive PCOS (21.7 and 52.2%, $P=0.009$) as well as HOMA-IR ≥ 2.7 (34.0 and 44.7%, $P=0.005$) and lipid accumulation index (LAP) ≥ 34.5 (35.7 and 50%, $P=0.013$). Active vs inactive controls also presented similar results ($P<0.05$). In conclusion, habitual physical activity, specifically walking 7500 or more steps daily, was associated with lower frequency of insulin resistance, assessed by different clinical markers in PCOS women. These data suggest that even a slight to moderate non-structured daily physical activity might bring health benefices in PCOS before metabolic comorbidities become evident.
Disclosure
This work was supported by grants from CNPq INCT 573747/2008-3 and FIPE-HCPA 12-0375, Brazil.
DOI: 10.1530/endoabs.37.GP.06.01

GP.06.02

Early diagnostics of insulin resistance in obese pregnant women

Oksana Kononova[1], Aleksej Korotaev[2], Erik Platoshkin[1], Andrej Pristrom[3] & Volha Vasilkova[1]
[1]Gomel State Medical University, Gomel, Belarus; [2]The Republican Research Centre for Radiation Medicine and Human Ecology, Gomel, Belarus; [3]Belarusian Medical Academy of Post-Graduate Education, Minsk, Belarus.

Aim
To find early diagnostic criteria for metabolic syndrome (MS) in obese women in early pregnancy.
Materials and methods
We examined 143 pregnant women aged from 19 to 43 years (31.0 (26.0; 35.0)) and divided them into three groups: MS group ($n=55$), risk group (one to two components of MS) ($n=57$), and control group ($n=31$). Laboratory examination included blood pressure (BP) monitoring, assessment of a lipid profile, glucose metabolism, and insulin resistance (HOMA-IR).
Results
76% of pregnant women with MS and 45% of pregnant women with one to two components of MS have obesity. Hypertension was diagnosed in 54 (64%) pregnant women. We found significant differences in systolic, diastolic, and pulse pressure between pregnant women with obesity and pregnant women without obesity ($P<0.001$). There were significant differences in level of fasting glucose, insulin and HOMA-IR, triglycerides, LDL-C, and VLDL-C in pregnant women with obesity comparing with pregnant women without obesity ($P<0.001$). Gestational diabetes (GD) was identified in the MS group up to 20 weeks in 18.2% of pregnant women, after 20 weeks in 29.1% of pregnant women. There were 10.5% of women with GD up to 20 weeks and 17.5% after 20 weeks in the risk group respectively. We found no disturbances in carbohydrate metabolism in 45.5% pregnant women from MS group and 71.9% from risk group.
Conclusion
Insulin resistance and its associated disorders of carbohydrate and lipid metabolism are common in obese women during pregnancy. Early identification of risk factors in obese pregnant women is a prerequisite for the prevention of serious complications in the future as part of the mother and the foetus.
DOI: 10.1530/endoabs.37.GP.06.02

GP.06.03

Characteristics of lipid profile in different phenotypes of polycystic ovary syndrome

Jelica Bjekic-Macut[1], Ivana Bozic Antic[2], Danijela Vojnovic Milutinovic[3], Dusan Ilic[2], Biljana Kastratovic-Kotlica[4], Olivera Stanojlovic[5], Zoran Andric[1] & Djuro Macut[2]
[1]CHC Bezanijska Kosa, Belgrade, Serbia; [2]Clinic of Endocrinology, Diabetes and Metabolic Diseases and Faculty of Medicine, University of Belgrade, Belgrade, Serbia; [3]IBISS, University of Belgrade, Belgrade, Serbia; [4]Clinic of Gynecology and Obstetrics, and Faculty of Medicine, University of Belgrade, Belgrade, Serbia; [5]Faculty of Medicine, Institute of Physiology, University of Belgrade, Belgrade, Serbia.

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

Methods
We evaluated 365 PCOS women (PCOS: 25.05 ± 6.24 kg/m^2; 25.48 ± 5.21 years) diagnosed using ESHRE/ASRM criteria and 125 BMI-matched healthy women (controls: 25.41 ± 5.16 kg/m^2; 30.35 ± 5.62 years). PCOS group was divided into four phenotypes: a (anovulation (ANOV), hyperandrogenism (HA), polycystic ovary morphology (PCOM)), B (ANOV, HA), C (HA, PCOM) and D (ANOV, PCOM). Phenotype D had lower BMI in comparison to all other phenotypes ($P<0.05$). Blood samples were collected in follicular phase of menstrual cycle for determination of total cholesterol (TC), LDL, HDL, triglycerides, apolipoprotein-A1 and apolipoprotein-B. Ratios TC/HDL, LDL/HDL, TG/HDL, apoliporotein-B/apolipoprotein-A1 were calculated.
Results
PCOS women in comparison to controls had higher levels of TC (5.07 ± 1.09 vs 4.89 ± 0.97 mmol/l, $P<0.001$), LDL (3.16 ± 0.97 vs 3.09 ± 0.82 mmol/l, $P=0.012$), TG (1.20 ± 0.85 vs 0.98 ± 0.54 mmol/l, $P<0.001$), apolipoprotein-B (0.88 ± 0.29 vs 0.83 ± 0.25, $P=0.021$), while there were no differences in HDL, apoliporpotein-A1 ($P>0.05$). PCOS women had higher ratios: TC/HDL (3.94 ± 1.36 vs 3.68 ± 1.03, $P=0.001$), LDL/HDL (2.46 ± 1.07 vs 2.36 ± 0.89, $P=0.019$), TG/HDL (1.02 ± 1.20 vs 0.78 ± 0.61, $P<0.001$), apoliporotein-B/apolipoprotein-A1 (0.59 ± 0.33 vs 0.52 ± 0.19, $P=0.011$). Comparisons between PCOS phenotypes revealed that phenotype D had lower levels of triglycerides and the ratio TG/HDL than other three phenotypes ($P<0.05$ for all comparisons), while there was no difference in other lipid concentrations and ratios. Phenotype A, B and C had higher TC, TG, TC/HDL, TG/HDL, and apoliporotein-B/apolipoprotein-A1 in comparison with controls, while there were no differences between phenotype D and controls.
Conclusion
In our group of women with PCOS, only phenotype D was characterised with less deteriorated lipid profile than other PCOS phenotypes.

DOI: 10.1530/endoabs.37.GP.06.03

GP.06.04

Phenotypic characteristic of type 1 diabetic women with polycystic ovary syndrome

Agnieszka Lebkowska[1], Agnieszka Adamska[1], Monika Karczewska-Kupczewska[2,3], Agnieszka Nikolajuk[3], Elzbieta Otziomek[1], Robert Milewski[4], Slawomir Wolczynski[5], Maria Gorska[1] & Irina Kowalska[1]
[1]Department of Endocrinology, Diabetology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland; [2]Department of Metabolic Diseases, Medical University of Bialystok, Bialystok, Poland; [3]Department of Prophylaxis of Metabolic Diseases, Institut of Animal Reproduction and Food Research, Polish Academy of Sciences, Olsztyn, Poland; [4]Department of Statistics and Medical Informatics, Medical University of Bialystok, Bialystok, Poland; [5]Department of Reproduction and Gynecological Endocrinology, Medical University of Bialystok, Bialystok, Poland.

Introduction
The prevalence of polycystic ovary syndrome (PCOS) is increased in women with type 1 diabetes (T1DM) in comparison to the general population. It has been suggested that exogenous insulin administered to T1DM women in supraphysiological doses could act as co-gonadotropin and lead to disturbances observed in PCOS.
Aim
The aim of this study was to evaluate the phenotypic characteristic and differences between diabetic women with PCOS (T1DM + PCOS) and age-, BMI-matched women with type 1 diabetes without PCOS (T1DM-no PCOS) and non-diabetic women with PCOS (PCOS).
Study participants and methods
We studied 108 women: 39 with T1DM (18 with T1DM + PCOS and 21 with T1DM-no PCOS), 47 with PCOS and 22 healthy women. PCOS was diagnosed using the Rotterdam criteria. The anthropometric measurements, clinical parameters, estimation of plasma concentrations of sex hormones, SHBG, HbA1c and ultrasonographic evaluation of the ovaries were performed for all women. In both diabetic groups insulin sensitivity was calculated with estimated glucose disposal rate (eGDR).
Results
There were no significant differences in anthropometric measurements between all studied groups. The Ferriman–Gallwey score was higher in women with PCOS than in those with PCOS + T1DM ($P=0.074$). Hormonal profile was similar in both groups with PCOS. We observed that ovarian volume and ovarian follicle count did not differ in patients with PCOS + T1DM and PCOS. The number of ovarian follicles was higher in the PCOS + T1DM and PCOS groups versus the control ($P=0.008$, $P<0.001$) and versus the T1DM/no-PCOS group ($P<0.001$, $P<0.001$, respectively). HbA1c, daily insulin dose, eGDR were not different between PCOS + T1DM and T1DM-no PCOS. A significant negative relationship of eGDR with body fat mass and BMI was found in T1DM + PCOS ($r=-0.75$, $P<0.001$; $r=-0.75$, $P<0.001$), which was not observed in patients with T1DM-no PCOS.
Conclusion
We conclude, that phenotypic characteristic of T1DM + PCOS women is similar to PCOS. Further study are required to better understand the pathogenesis of PCOS in type 1 diabetic women.
Disclosure
This work was supported by the Medical University of Bialystok in Poland (grant number 123-50722L).

DOI: 10.1530/endoabs.37.GP.06.04

GP.06.05

Cytokine expression in SAT and VAT from PCOS patients and control women; possible proinflammatory effect of testosterone depending on BMI – a preliminary report

Nicolas Crisosto[1], Barbara Echiburú[1,2], Francisco Perez-Bravo[2], Cristian Flores[1,2], Cecilia Fuentes[3], Mariana Cifuentes[3], Omar Orellana[4], Fernando Maluenda[5] & Teresa Sir-Petermann[1]
[1]Laboratory of Endocrinology and Metabolism, Faculty of Medicine, West Division, University of Chile, Santiago, Chile; [2]Laboratory of Nutritional Genomics, Department of Nutrition, Faculty of Medicine, University of Chile, Santiago, Chile; [3]Basic Nutrition and Genetic Epidemiology Laboratory Institute of Nutrition and Food Technology (INTA), University of Chile, Santiago, Chile; [4]Surgery Unit, Hospital San Juan de Dios, Santiago, Chile; [5]Surgery Unit, Clinica Las Condes, Santiago, Chile.

Context
Insulin resistance is an important component of polycystic ovary syndrome (PCOS). Local cytokine production in adipose tissue increases local insulin resistance. The effect of testosterone on local adipose tissue cytokine production has not been explored thoroughly.
Aim
To evaluate cytokine expression in subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) from PCOS and control women and evaluate the response to testosterone on the later.
Methodology
We obtained serum samples and SAT by biopsy from ten PCOS and seven control women. In six different women (three PCOS and three controls) subjected to abdominal surgery we obtained samples from omental VAT that were incubated (300 mg each well) for 72 h in basal conditions or stimulated with 10-9M or 10-6 M testosterone (T). Expression of cytokines (I-1b, CCL-2, TNF-alpha and IL-6) in tissue samples was assessed by Real Time PCR. All women studied were 18–40 years old.
Results
Basal SAT and VAT cytokine expression and serum cytokine levels showed no differences between PCOS and control patients. Regarding stimulated tissue samples, there was no significant response to T in the total group or analysing PCOS or control patients independently. Nevertheless, in VAT samples from patients with a BMI between 30 and 40, regardless of their PCOS condition, we found a significant increase in the expression of CCl-2 (ddCt 1,83 (1.75–1.96; $P=0.0036$) and IL1b (ddCt:2.84 (2.52–3.7; $P=0.0036$) when stimulated with testosterone 10–6M.
Conclusions
SAT and VAT shows no significant differences in terms of basal cytokine expression between PCOS patients and control women. Nevertheless, in the subgroup of women with a BMI between 30 and 40, testosterone seems to have a proinflammatory effect in VAT. Thus, the effects of testosterone in terms of cytokine expression might be influenced by the presence of obesity.
Disclosure
This work was supported by FONDECYT INICIACION grant 11130126 and FONDECYT grant 1110864.

DOI: 10.1530/endoabs.37.GP.06.05

GP.06.06

Does finasteride, as well as metformin, improve insulin resistance in PCOS?

Halit Diri, Fahri Bayram & Yasin Simsek
Division of Endocrinology, Erciyes University Medical School, Kayseri, Turkey.

Introduction
The effects of finasteride on insulin resistance and of metformin on hyperandrogenism in patients with polycystic ovary syndrome (PCOS) are not clear. This study therefore compared the effects of finasteride, metformin, and finasteride plus metformin treatments on hormone levels, insulin resistance, and hirsutism score in women with PCOS.
Subjects and method
Fifty-two patients with PCOS were randomly assigned to receive finasteride 5 mg/day, metformin 1700 mg/day or finasteride plus metformin for 12 months. BMI, Ferriman Gallway score (FGS), serum concentrations of estradiol, sex hormone-binding globulin, free testosterone, DHEAS, androstenedione, and HOMA-IR index and areas under the curve (AUC) for insulin and glucose were evaluated before and after 12 months of treatment.
Results
Reductions in FGS, free testosterone, DHEAS, androstenedione, HOMA-IR, AUC-insulin, and AUC-glucose were significant within each group, whereas BMI and estradiol did not. Comparisons of changes in parameters in the three groups did not clearly show the superiority of any treatment modality.
Discussion
Insulin resistance and hyperandrogenism are the two major interacting pathophysiological derangements in PCOS. Thus, treatment with finasteride alone should significantly reduce both androgen levels and parameters of insulin resistance; and our results confirmed that suggestion. In addition, metformin alone was effective, and not inferior to finasteride, in the treatment of hyperandrogenism.
Conclusion
The finasteride, metformin, and their combination therapies were effective and safe in women with PCOS, since both drug classes have beneficial effects on both hyperandrogenism and insulin resistance.

DOI: 10.1530/endoabs.37.GP.06.06

GP.06.07

The effect of metformin and liraglutide on markers of subclinical atherosclerosis in women with polycystic ovary syndrome

Mojca Jensterle[1], Mateja Kaja Jezovnik[2], Ana Spirkoska[2], Pavel Poredos[2] & Andrej Janez[1]
[1]Department of Endocrinology, Diabetes and Metabolic Diseases, University Medical Centre Ljubljana, Ljubljana, Slovenia; [2]Department of Vascular Disease, University Medical Centre Ljubljana, Ljubljana, Slovenia.

Subclinical atherosclerosis is frequently present in women with polycystic ovary syndrome (PCOS). Metformin and liraglutide both improve metabolic control in PCOS, however they might exert different anti-atherosclerotic effects. We investigated the impact of these medications on the subclinical atherosclerotic changes of the arterial wall in PCOS patients.
Methods
72 women with PCOS (aged 28.6 ± 6.3 years, BMI 38.4 ± 5.0 kg/m^2, mean $\pm$ S.D.) were assigned to therapy with either metformin 1 g BID or liraglutide 1.2 mg QD sc. for 12 weeks. Markers of subclinical atherosclerosis including intima-media thickness (IMT), flow-mediated dilation (FMD), low-flow-mediated constriction (L-FMC), and peripheral tonometry (PAT) with pulse wave amplitude (PWA) were measured. Arterial stiffness was investigated through pulse wave velocity (PWV) and the augmentation index (AI). All measurements were obtained at baseline and at study end.
Results
25 patients on metformin and 40 patients on liraglutide completed the study. Metformin improved FMD from 7.33 ± 3.11 to $9.12 \pm 2.75\%$ ($P=0.04$). Liraglutide decreased IMT from 0.53 ± 0.06 to 0.50 ± 0.05 mm ($P=0.04$), arterial stiffness as assessed by AI from 31.4 ± 7.8 to 39.6 ± 13.1 ($P=0.03$) and also caused a border-line, non-significant improvement of PWA ($P=0.07$). Furthermore, there was a significant inverse relationship between FMD and HOMA index before and after treatment in both arms ($r=0.61$, $P<0.05$).
Conclusions
Short-term intervention with metformin and liraglutide have beneficial effect on markers of subclinical atherosclerosis in obese women with PCOS. Interestingly, the effects of metformin therapy resulted only in functional improvement, whereas liraglutide also ameliorated morphological signs of atherogenesis of the arterial wall.

DOI: 10.1530/endoabs.37.GP.06.07

GP.06.08

Plasma brain derived neurotrophic factor is decreased in women with polycystic ovary syndrome and related to the markers of endothelial dysfunction

Irina Kowalska[1], Monika Karczewska-Kupczewska[2,3], Agnieszka Adamska[1], Agnieszka Nikolajuk[2,3], Agnieszka Lebkowska[1], Elzbieta Otziomek[1], Slawomir Wolczynski[4] & Marek Straczkowski[2,3]
[1]Department of Endocrinology, Diabetology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland; [2]Department of Metabolic Diseases, Medical University of Bialystok, Bialystok, Poland; [3]Department of Prophylaxis of Metabolic Diseases, Institute of Animal Reproduction and Food Research, Polish Academy of Sciences, Olsztyn, Poland; [4]Department of Reproduction and Gynecological Endocrinology, Medical University of Bialystok, Bialystok, Poland.

Introduction
Brain derived neurotrophic factor (BDNF) is a neurotrophin which plays a role in neuronal growth and differentiation. Decreased level of BDNF is supposed to play a role in the pathogenesis of the neurodegenerative diseases. Recent data indicate that BDNF could be also involved in angiogenesis. Several lines of evidence support the role of BDNF in glucose metabolism. The decreased level of BDNF are observed in obesity and type 2 diabetes mellitus. Polycystic ovary syndrome (PCOS) is a common endocrine disorder associated with insulin resistance and increased risk of cardiovascular diseases. The aim of the present study was to determine plasma BDNF concentration in patients with PCOS in comparison to healthy women.
Study participants and methods
We studied 74 women with PCOS (BMI -27.60 ± 6.73 kg/m^2) and 37 healthy, regularly menstruating women (BMI -26.69 ± 6.72 kg/m^2). PCOS was diagnosed with Rotterdam criteria. Clinical examination, an anthropometric measurements, hyperinsulinaemic, euglycaemic clamp and estimation of plasma concentrations of BDNF, sex hormone binding globulin (SHBG), adiponectin, soluble E-selectin (sE-selectin), intercellular adhesion cell molecule-1 (sICAM-1), hormonal and lipid profile were performed in all study participants.
Results
Women with PCOS had significantly higher LH ($P<0.0001$), testosterone ($P=0.011$) and FAI ($P=0.04$) in comparison to the control group. Plasma BDNF concentration was lower in PCOS group vs controls ($P=0.04$). Subgroups analysis revealed that plasma BDNF was significantly lower in the obese PCOS women vs obese controls ($P=0.03$), whereas such difference was not found between lean PCOS and control women. In PCOS group, plasma BDNF correlated significantly with SHBG ($r=0.26$, $P=0.02$), adiponectin ($r=0.29$, $P=0.012$), sICAM-1 ($r=-0.28$, $P=0.014$) and sE-selectin ($r=-0.24$, $P=0.03$), which was not observed in the control group.
Conclusion
Our data indicate that BDNF is decreased in obese PCOS women and related to the markers of endothelial dysfunction.
Disclosure
This study was supported by the grant from the Medical University of Biał, Poland – 113-50740L

DOI: 10.1530/endoabs.37.GP.06.08

Reproduction: Female and other

GP.07.01

Preconceptional TSH and miscarriage in infertile women submitted to IVF

Guia Vannucchi[1], Danila Covelli[1], Mario Renzini[3], Claudio Brigante[3], Giovanni Coticchio[3], Maria Beatrice Dal Canto[3], Rubens Fadini[3], Davide Dazzi[4], Roberto Negro[5] & Laura Fugazzola[1,2]
[1]Endocrine Unit, Fondazione IRCCS Cà Granda, Milan, Italy; [2]Department of Transplant, University of Milan, Milan, Italy; [3]Center of Reproduction Medicine Biogenesi, Istituti Clinici Zucchi, Monza, Italy; [4]Internal Medicine, Ospedale di Fidenza, Fidenza, Italy; [5]Division of Endocrinology, 'V. Fazzi' Hospital, Lecce, Italy.

It is known that high levels of TSH are associated with higher miscarriage risk, though the precise TSH cut-offs are debated. Aim of the present study was to evaluate if pre-conceptional TSH levels associate with increased risk of early miscarriage in a large series of infertile women submitted to IVF and to determine the threshold of TSH associated with the highest prevalence of pregnancy loss. We retrospectively studied 1484 infertile women (mean ± age 36.7 ± 4.1 years, mean ± s.d. BMI 22.7 ± 4) submitted to IVF in a single center from 2004 to 2014.
Overall, 371/1484 (25%) patients had a biochemical pregnancy and 152 of them experienced a pregnancy loss. Mean TSH levels of women with a regular pregnancy were significantly lower than mean TSH levels recorded in patients with a pregnancy loss (1.8 ± 0.8 vs 2.2 ± 1.2, $P=0.01$). Interestingly, the miscarriage rate was progressively higher for increasing TSH cut-off levels ($\leq$2.5 vs $>$2.5 $P=0.08$; $\leq$3 vs $>$3 $P=0.001$; $\leq$4.5 vs $\geq$4.5 $P=0.004$). Moreover, among the 152 women with pregnancy loss, 59 (39%) were clinically pregnant and had a miscarriage in the first trimester, while in 93 patients (61%) a biochemical pregnancy without clinical evolution was documented, but no significant differences in mean TSH levels were recorded between women with different time of miscarriage.
In conclusion, in women undergoing IVF, lower TSH levels reduce the risk of early pregnancy loss. These data strongly indicate the need for TSH screening prior to IVF procedures, and suggest the treatment of women with TSH levels $>$3 mU/l.

DOI: 10.1530/endoabs.37.GP.07.01

GP.07.02

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

Daniela Fernandois, Ruth Márquez, Hernán Lara & Alfonso Paredes
Laboratory of Neurobiochemistry, Department of Biochemistry and Molecular Biology, Faculty of Chemical and Pharmaceutical Sciences, University of Chile, Santiago, Chile.

Kisspeptin is found in the ovary of different species including human and rat. We have recently described, through *in vitro* studies, that kisspeptin is under the control of sympathetic innervation of the ovary. Considering that ovarian activity of sympathetic nerves increases with ageing, it is possible that the ovarian kisspeptin also increases during this period. As a role of kisspeptin in folliculogenesis has been postulated, this increase in kisspeptin could participate in the changes in follicular dynamics that occur during the subfertility period. We conducted an *in vivo* study to determine if the ovarian sympathetic tone participates in kisspeptin expression during reproductive ageing. To achieve this, we measured kisspeptin mRNA and protein levels by qRT-PCR and western-blot at 6, 8, 10 and 12 months old rats, covering fertile (6 month), subfertile (8 and 10 months) and infertile periods (12 months). We also performed an *in vivo* blockade of β-adrenergic receptor with propranolol (5 mg/kg) and an ovarian surgery denervation to modulate sympathetic system at these ages. The non-treated rats showed an increase in kisspeptin expression at 10 and 12 months old ($P<0,05$) compared to 6 months old rats, and if we compared this kisspeptin levels with the noradrenaline content, we observed an almost perfect correlation ($r=0.994$). Ovarian kisspeptin peptide decreased both, after propranolol administration and with the surgical denervation ($P<0.01$ 8 to 12 months compared with 6 months). These results suggest that intraovarian kisspeptin is regulated by sympathetic nerve via β-adrenergic receptor, participating locally in the ovary function and that ovarian kisspeptin could participate in follicular development with noradrenaline in reproductive ageing.

Disclosure
Fondecyt 1120147, Proyecto Gastos Operacionales y Beca Doctorado Nacional 21120454.

DOI: 10.1530/endoabs.37.GP.07.02

GP.07.03

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

Sunmie Kim[1], Kyu Ri Hwang[2], Jin Ju Kim[1], Min-Jeong Kim[1] & Seok Hyun Kim[3]
[1]Department of Obstetrics and Gynecology, Healthcare Research Institute, Healthcare System Gangnam Center, Seoul National University Hospital, Seoul, Republic of Korea; [2]Department of Obstetrics and Gynecology, Seoul Municipal Boramae Hospita, Seoul, Republic of Korea; [3]Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, Republic of Korea.

Objective
The aim of our study is to determine clinical factors and sonographic findings associated with endometrial hyperplasia or cancer (EH+) in pre- and perimenopausal women.
Study design
A total of 14 340 transvaginal ultrasonography examinations of 9 888 healthy pre- and perimenopausal women were included in this retrospective study. One hundred sixty-two subjects underwent endometrial biopsy based on abnormal uterine bleeding (AUB), sonographic endometrial abnormalities (thickened endometrium, endometrial mass, or endometrial stripe abnormality), or both. The clinical factors and sonographic endometrial abnormalities were evaluated with regard to EH+.
Results
Histologically verified EH+ was found in fourteen subjects (8.6%); ten cases of endometrial hyperplasia without atypia (EH), three cases of endometrial hyperplasia with atypia (AEH), and one case of endometrial cancer. Neither clinical factors nor AUB were associated with EH+ ($P=0.32$) or AEH+ ($P=0.72$). Of sonographic findings, endometrial stripe abnormality was significantly associated with EH+ ($P=0.003$) and marginally associated with AEH+ ($P=0.05$), but a thickened endometrium was not associated with EH+ ($P=0.43$).
Conclusion
Endometrial stripe abnormality is a significant factor to predict EH+ in healthy pre- and perimenopausal women with and without AUB. However, simple measurement of endometrial thickness has a limited role in this capacity.

DOI: 10.1530/endoabs.37.GP.07.03

GP.07.04

Expression of melanocortin receptors in human endometrium

Anastasia Lantang[1,2], Earn Gan[2], Barbara Innes[1], Simon Pearce[1] & Gendie Lash[2]
[1]Reproductive and Vascular Biology Group, Institute of Cellular Medicine, Newcastle University, Newcastle Upon Tyne, UK; [2]Institute of Genetic Medicine, Newcastle University, Newcastle Upon Tyne, UK.

Background
The melanocortin system is known to be involved in hypothalamic regulation of energy balance, which is implicated in reproductive success. However, the peripheral role for melanocortin receptor (MCR) signalling in the reproductive system has not been described. During a clinical trial of repeated high dose tetracosactide ($ACTH_{1-24}$) injection, four of nine premenopausal women with Addison's disease developed menstrual disturbances. We wondered if these adverse effects were mediated via direct melanocortin signalling in human endometrium, which has not been previously examined.
Methods
Endometrial ($n=8$) biopsies were obtained from pre-menopausal women after hysterectomy for non-endometrial pathology. Decidual (8–10 weeks gestation; $n=5$) tissues were obtained after termination of apparently normal pregnancies. The localisation of the expression of melanocortin receptors (MCR 1-5) in the human endometrium was performed using immunocytochemistry. Tissue culture was used to characterise the effects of $ACTH_{1-24}$ on decidual tissue and blood vessel integrity determined by immunostaining for vascular smooth muscle cell (VSMC) markers.

Results
Robust expression of MC5R was demonstrated in human endometrium. Moderate to strong MC2R and MC3R expressions were also shown in this tissue. Expression of MC1R and MC4R was negligible. A dose-dependent reduction in VSMC in the cultured decidual tissue's vessel wall was observed during treatment with high concentrations of $ACTH_{1–24}$. However, the difference was only significant after treatment with the highest concentration of ACTH (500 ng/ml) ($P = 0.03$).
Conclusion
Our study demonstrated for the first time MC2R, MC3R and MC5R expression in human endometrium at the protein level. These melanocortin receptors may play a role in regulating endometrial proliferation or integrity, which could mediate menstrual disturbances observed in the clinical trial. Understanding of melanocortin receptors' role in the uterus and decidual tissue could potentially inform the pathogenesis of uterine dysfunction. The effects of ACTH excess or deficiency on the endometrium via melanocortin signalling should also be explored further.

DOI: 10.1530/endoabs.37.GP.07.04

GP.07.05

mRNA expressions of skin steroidogenic enzymes in women with idiopathic hirsutism

Serpil Taheri[1], Kursad Unluhizarci[2], Gokmen Zararsiz[3], Sulbiye Karaburgu[1], Murat Borlu[4], Tuncay Ozgun[5], Zuleyha Karaca[2], Fatih Tanriverdi[2], Munis Dundar[1] & Fahrettin Kelestimur[2]
[1]Department of Medical Genetics, Erciyes University Medical School, Kayseri, Turkey; [2]Department of Endocrinology, Erciyes University Medical School, Kayseri, Turkey; [3]Department of Biostatistics, Erciyes University Medical School, Kayseri, Turkey; [4]Department of Dermatology, Erciyes University Medical School, Kayseri, Turkey; [5]Department of Obstetrics and Gynecology, Erciyes University Medical School, Kayseri, Turkey.

Introduction
The pathogenesis of idiopathic hirsutism (IH) is not clear. On the other hand, human skin possesses all the enzymes necessary for androgen synthesis and catabolism indicating that it is an independent peripheral endocrine organ. Thus, in the present study we aimed to investigate the mRNA expression of aromatase enzyme and the other enzymes having functional roles in the steroidogenic pathway, in freshly obtained skin tissue from subumblical skin and the arm of women with IH.
Patients
We aimed to determine mRNA expressions of genes associated with local androgen synthesis and metabolism (CYP11A1, STS, CYP19A1, SRD5A1, SRD5A2, HSD3B1, AR, COMT, ESR1, ESR2, HSD3B2, CYP17A1, SULT2A1, SULT1E1, HSD17B2, IL6, TGFβ1, TNF-α) from skin biopsy and blood samples of 21 patients with IH and the data compared with 15 healthy subjects.
Results
We found that patients with IH exhibit significantly lower expression of IL-6 mRNA and higher steroid sulphatase (STS) and HSD17B2 gene mRNA expression, respectively, in the subumblical region skin biopsies. Similarly, patients with IH exhibit significantly lower IL-6 mRNA expression and higher STS and HSD17B2 gene mRNA expression, respectively, in the arm skin compared to healthy women's subumblical region. There were no significant differences in any gene expression between the arm and subumblical skin biopsies in the patient group. In addition, there were no significant differences in any gene expression in peripheral blood mononuclear cells of the patients and healthy women.
Discussion
Our results suggest that the increased mRNA expression of HSD17B2 and STS genes, decreased IL6 mRNA are not dependent on circulating levels of testosterone. In both arm and umblical skin biopsy of patients with idiopathic hirsutism, we observed an up-regulation of HSD17B2 and STS, decreased IL6, probably determining an increase in the local amount of active androgens, which could then be used as substrate for other androgen metabolic routes.
Disclosure
This work was supported by hte Erciyes University Research Council (TSA-12-4053).

DOI: 10.1530/endoabs.37.GP.07.05

GP.07.06

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

Lina Ciaplinskiene, Dalia Kozloviene, Robertas Knispelis, Ruta Kriksciuniene, Rimas Zalinkevicius & Birute Zilaitiene
Lithuanian University of Health Sciences, Kaunas, Lithuania.

Inconsistences in hirsutism evaluation using The Modified Ferriman-Gallwey scale (mFG) between different evaluators and need for hirsutism diagnostics standardization has been reported in numerous publications.
The aim of the study was to determine the differences in the evaluation of female hirsutism between researchers.
Materials and methods
The study was conducted during the period March to June of 2013. The study was carried out by six physicians – one specialist in female hyperandrogenism (an expert physician), and five – with no such experience. At the beginning of the study, the expert physician trained other researchers in the evaluation of terminal hair growth using mFG scale. The study included 90 women who presented to the endocrinologist's consultation due to different reasons except hyperandrogenism and met the inclusion criteria. The subjects underwent anthropometric measurements, and were asked to perform self-evaluation of hirsutism according to the mFG scoring method. Following that, hirsutism was evaluated by the physicians-researchers using the same mFG scoring method.
Results
The study included healthy 20–34 year old (mean age 25.2 years, 95% CI 23.8–26.5) women with regular menstrual cycles. The total mean score of the subjects' self-evaluation was 7.0, 95% CI 4.6–9.3. The total mean score of the evaluation given by the researchers was 2.81, 95% CI 1.5–4.2. The odds ratio for erroneous evaluation of hirsutism on the upper lip was 1.31 (95% CI 1.02–1.69), on the lower abdomen and the thigh – 5.44 (95% CI 4.23–7.02), and on the chest – 0.02 (95% CI 0.02–0.04).
Conclusions
A discrepancy was found between the evaluations submitted by the expert physician and one of evaluators, whereas the differences between the evaluations presented by the other researchers were not significant. The women who participated in the study significantly more frequently submitted higher mFG scores when evaluating their hirsutism than the researchers did. The greatest differences between the evaluations of hirsutism were found on the upper lip, the lower abdomen, and thighs. Extensive training is needed before starting use The Modified Ferriman-Gallwey scale in order to get reliable results of hirsutism evaluation.

DOI: 10.1530/endoabs.37.GP.07.06

GP.07.07

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

Sandra Mrozinska[1], Tomasz Milewicz[2], Iwona Rogatko[3], Marta Kialka[4], Magdalena Spalkowska[5], Kamila Migacz[6], Aleksandra Kowalczuk[7], Agnieszka Kawula[8] & Anna Galuszka-Bednarczyk[9]
[1]Department of Endocrinology, Collegium Medicum, Jagiellonian University, Cracow, Poland; [2]Department of Gynecological Endocrinology, Collegium Medicum, Jagiellonian University, Cracow, Poland; [3]Department of Clinical Biochemistry, Polish-American Institute of Pediatrics, Cracow, Poland; [4]Department of Gynecological Endocrinology, Collegium Medicum, Jagiellonian University, Cracow, Poland; [5]Department of Dermatology, Collegium Medicum, Jagiellonian University, Cracow, Poland; [6]Department of Gynecological Endocrinology, Collegium Medicum, Jagiellonian University, Cracow, Poland; [7]Department of Gynecological Endocrinology, Collegium Medicum, Jagiellonian University, Cracow, Poland, [8]Specialist Hospital, Rybnik, Poland; [9]Department of Gynecological Endocrinology, Collegium Medicum, Jagiellonian University, Cracow, Poland.

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

(PCOS), known as the state with increased testosterone level. This paper considers a possible relationship between the level of free androgen index (FAI) and glucose-dependent insulinotropic peptide (GIP) among lean women affected by PCOS. To our knowledge, no previous study has evaluated the matter so far.
Case control study
50 lean women (BMI = 20.76 ± 1.83) were enrolled to the study and divided into two groups according to the FAI level. Group A consisted of 25 patients with FAI <5 and group B consisted of 25 patients with FAI >5. All subjects underwent standard meal test. Serum GIP concentration was determined both at fasting and at 60 min of the test. Calculations were computed in the Statistica Program.
Results
Mean GIP was significantly higher in group 2 before and after meal test (Mann-Whitney's U test; $P=0.006$). Likewise, group 2 exhibited higher values of medians. Spearman's test indicated significant correlation between FAI and GIP levels at $0'$ and $60'$ in total study population ($0'$: $P=0.008$; $60'$: $P=0.049$). The absence of the significant correlation was observed in each group. It might be a consequence of the limited number of patients.
Conclusion
Excess androgen activity might be a vital factor contributing to alter secretion of incretins in lean PCOS women. An increased GIP levels may induce hyperinsulinaemia and play an additive to insulin resistance role in progression to T2DM.

DOI: 10.1530/endoabs.37.GP.07.07

Reproduction: Male and endocrine disruptors

GP.08.01

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

Tomas B Ahern[1], Ilpo T Huhtaniemi[2], Emma L Carter[1], Joseph D Finn[1], Stephen R Pye[3], Terence W O'Neill[3], Gyorgy Bartfai[4], Felipe F Casanueva[5], Gianni Forti[6], Aleksander Giwercman[7], Thang S Han[8], Krzysztof Kula[9], Michael EJ Lean[10], Neil Pendleton[11], Margus Punab[12], Dirk Vanderschueren[13] & Frederick C W Wu[1]
[1]Andrology Research Unit, Centre for Endocrinology and Diabetes, Institute of Human Development, The University of Manchester, Old St Mary's Building, Manchester, UK; [2]Department of Surgery and Cancer, Institute of Reproductive and Developmental Biology, Imperial College London, Hammersmith Campus, London, UK; [3]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, UK; [4]Department of Obstetrics, Gynaecology and Andrology, Albert Szent-György Medical University, Szeged, Hungary; [5]Department of Medicine, Santiago de Compostela University, Complejo Hospitalario Universitario de Santiago (CHUS), CIBER de Fisiopatología Obesidad y Nutricion (CB06/03), Instituto Salud Carlos III, Santiago de Compostela, Spain; [6]Andrology Unit, Department of Clinical Physiopathology, University of Florence, Florence, Italy; [7]Reproductive Medicine Centre, Malmö University Hospital, University of Lund, Lund, Sweden; [8]Department of Endocrinology, Royal Free and University College Hospital Medical School, Royal Free Hospital, Hampstead, London, UK; [9]Department of Andrology and Reproductive Endocrinology, Medical University of Łódź, Lodz, Poland; [10]Department of Human Nutrition, University of Glasgow, Glasgow, UK; [11]School of Community Based Medicine, Hope Hospital, The University of Manchester, Salford, UK; [12]Andrology Unit, United Laboratories of Tartu University Clinics, Tartu, Estonia; [13]Department of Andrology and Endocrinology, Katholieke Universiteit Leuven, Leuven, Belgium.

Introduction
Primary hypogonadism (PHG, testosterone <10.5 nmol/l and LH >9.5 U/l) without a recognisable cause affects ~2% of community-dwelling middle-aged and older men. We sought to identify the clinical significance of, and risk factors for, this apparently age-related hypogonadal state.
Methods/design
The European Male Ageing Study (EMAS) is a prospective observational cohort survey of 3.369 community-dwelling men aged 40–79 in eight European countries who underwent follow up assessment an average of 4.3 years later. Men were classified as incident i) PHG (Eugonadal (EUG) at baseline, PHG at follow-up) or persistent (p) PHG (PHG at baseline and at follow-up), and were compared to those with pEUG (EUG at baseline and at follow-up). Differences in clinical and laboratory parameters between the groups and potential risk factors for iPHG were assessed using descriptive statistics and regression models.
Results
Of the 1.996 men comprising the analytical sample, 1.946 (97.5%) had pEUG, 23 (1.15%) had iPHG, 22 (1.10%) pPHG, and 5 (0.25%) reverted to EUG. The incidence of PHG was 0.27%/year. At baseline, iPHG (compared to pEUG) men were on average 9 years older ($P<0.001$), more likely to be smokers (OR 5.9 (1.8–18.6); $P=0.003$) and tended to have more illnesses (OR 2.8 (0.9–8.5); $P=0.069$). Their baseline total and free T levels were lower, and gonadotropin levels higher than in pEUG men. Upon transition from EUG to PHG, the characteristics which worsened significantly included erectile dysfunction, walking limitation, haemoglobin, self-rated physical function and frequency of >2 illnesses. Clinical parameters in iPHG and pPHG at follow-up were in the main similar.
Conclusion
PHG is a relatively rare condition in ageing men. The major risk factors for its development include older age, smoking and chronic illness. PHG in ageing men is characterised by clinical features compatible with both androgen deficiency and deteriorating functional health.
Disclosure
The European Male Ageing Study is funded by the Commission of the European Communities Fifth Framework Programme 'Quality of Life and Management of Living Resources' Grant QLK6-CT-2001-00258.

DOI: 10.1530/endoabs.37.GP.08.01

GP.08.02

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

Alberto Ferlin[1], Marco D'Aurora[2], Marta Di Nicola[3], Andrea Garolla[1], Luca De Toni[1], Sara Franchi[2], Giandomenico Palka[4], Carlo Foresta[1], Liborio Stuppia[2] & Valentina Gatta[1]
[1]Department of Medicine, University of Padova, Padova, Italy; [2]Department of Psychological, Humanities and Territorial Sciences, 'G.d'Annunzio' University, Chieti, Italy; [3]Department of Experimental and Clinical Sciences, 'G.d'Annunzio' University, Chieti, Italy; [4]Department of Oral Health and Biotechnological Sciences, 'G.d'Annunzio' University, Chieti, Italy.

Background
Klinefelter syndrome (KS) is the most common abnormality of sex chromosomes (47,XXY) and represents the first genetic cause of male infertility. Mechanisms leading to KS testis degeneration are still not completely defined but considered to be mainly the result of germ cells loss. In order to unravel the molecular basis of global testis dysfunction in KS patients, we performed a transcriptome analysis on testis biopsies obtained from six azoospermic non-mosaic KS patients and three control subjects.
Results
The analysis found that, compared to controls, KS patients showed the differential up- and down-expression of 656 and 247 transcripts. The large majority of the deregulated transcripts were expressed by Sertoli cells (SCs) and Leydig cells (LCs). Functional analysis of the deregulated transcripts indicated changes of genes involved in cell death, inflammatory response, lipid metabolism, steroidogenesis, blood-testis-barrier (BTB) formation and maintenance, as well as spermatogenesis failure.
Conclusions
Taken together, the present data highlight the modulation of hundreds of genes in the somatic components the testis of KS patient. The increased LCs steroidogenic function together with the impairment of inflammatory pathways and BTB structure, result in increased apoptosis. These findings might represent a critical roadmap for therapeutic intervention and prevention of KS-related testis failure.
Disclosure
This work was supported by Italian Ministry of Research.

DOI: 10.1530/endoabs.37.GP.08.02

GP.08.03

Infertile men have frequently Leydig cell dysfunction: study on hypogonadism, vitamin D and bone mass in 5177 subjects

Alberto Ferlin, Andrea Garolla, Riccardo Selice, Nicola Caretta, Damiano Pizzol & Carlo Foresta
Department of Medicine, University of Padova, Padova, Italy.

Spermatogenic disruption is normally recognized by low sperm count and FSH levels. However, Leydig cell impairment is also frequent in subjects with primary testicular damage, as evidenced for example by reduced INSL3 and 25(OH)-vitamin D levels. The latter is caused by reduced expression of CYP2R1, a major enzyme involved in 25-hydroxylation of cholecalciferol. Furthermore, testosterone (T) production by the Leydig cells might be also impaired in men with primary spermatogenic damage. To clarify these we evaluated the presence and type of hypogonadism, 25(OH)-vitamin D status and bone mass in a very large cohort of infertile males. Among subjects referred to our tertiary Universitary Centre for semen analysis during the period January 2011 to June 2014 (11 516 semen analysis) we report here the data of men who completed the andrological program, including semen culture (*n*: 10 394), history and physical examination (*n*: 7527), hormone analysis (FSH, LH, T, 25(OH)-vitamin D; *n*: 5884), and ultrasound of the testes (*n*: 5177). Men with total sperm count <10 million/ejaculate (*n*: 2583) underwent also genetic analysis (karyotype, Yq microdeletions, CFTR mutations; *n*: 2273) and DXA (*n*: 855). Azoospermia was present in 9.3% of cases, oligozoospermia (with or without reduced motility and/or normal sperm morphology) in 40.6%, asthenozoospermia in 12.2%, and normozoospermia in 34.5%. Main causes or risk factors were varicocele (28%), genetics (15%), obstruction/sub-obstruction of seminal tract (12%), cryptorchidism (6%), infections/iatrogenic causes/ejaculation disorders/prior surgery (14%) and idiopathic forms (25%). Primary hypogonadism ($T<10.4$ nmol/l, LH >8 IU/l) was found in 25.7% of cases, secondary hypogonadism ($T<10.4$ nmol/l, LH <1.5 IU/l) in 1.3%, subclinical hypogonadism ($T>10.4$ nmol/l, LH >8 IU/l) in 34.2%. Men with all forms of hypogonadism have frequently insufficient (48.5%) or deficient (25.4%) 25(OH)-vitamin D levels and higher risk of low bone mass, osteoporosis (16.8%) and osteopenia (31.5%). This study showed that hypogonadism and low vitamin D levels are very frequent in infertile males. Both conditions are implicated in the frequent low bone mass seen in these patients. Metabolic and other clinical conditions associated with low T and low vitamin D levels need therefore to be accurately evaluated in these subjects, and treatment should consider also these aspects.

DOI: 10.1530/endoabs.37.GP.08.03

GP.08.04

Triclosan-induced breast cancer growth was antagonised by kaempferol, a phytoestrogen, via regulating cell cycle, migration and apoptosis related genes in MCF-7 breast cancer cells

Seung-Hee Kim, Kyung-A Hwang & Kyung-Chul Choi
Laboratory of Biochemistry and Immunology, College of Veterinary Medicine, Chungbuk National University, Cheongju, Chungbuk, Republic of Korea.

Triclosan (TCS) is one of endocrine disrupting chemicals (EDCs) derived from toothpastes, deodorant and cleaning supplies. As a phytoestrogen, kaempferol (Kaem) is found at variety of vegetables. In this study, we examined anti-proliferative effects of Kaem in TCS-induced cell growth in MCF-7 breast cancer cells. In MTT assay, TCS (10^{-6} M) increased the cell viability of MCF-7 cells, while Kaem (50 μM) significantly reduced the cell viability compared to a control (0.1% DMSO). Kaem reversed TCS-induced MCF-7 cell growth at 50 μM. To confirm that Kaem inhibited TCS-induced cell growth, we examined the transactional levels of cell growth and apoptosis-related markers using reverse transcription (RT)-PCR. The expression levels of cyclin D, cyclin E and were increased, while that of p21 and bax mRNAs was decreased by TCS in MCF-7 cells. In addition, Kaem treatment significantly reversed TCS-induced gene expressions. In parallel with its mRNA level, the protein level of cyclin E, cyclin D, cathepsin D, p-IRS1, p-AKT, p-ERK and p-MEK1/2 were induced by TCS while it was reversed by Kaem. The expression levels of p21 and bax genes was altered by TCS and reversed by Kaem treatment. For *in vivo* assay, a xenografted mouse model was generated following injection with MCF-7 breast cancer cells. In parallel with *in vitro* results, tumour volumes following treatment with E_2 and TCS were continually increased compared to a vehicle (corn oil). It was of interest that treatment of the mice with combination of E_2 plus Kaem or TCS plus Kaem showed less tumour formation rather than that of single treated mice with E_2 or TCS. Taken together, these results indicate that Kaem may inhibit the growth MCF-7 cells via regulating the expression of cell cycle, migration and apoptosis-related genes, suggesting that TCS-induced progression of breast cancer may be suppressed by a phytoestrogen (This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (MEST) of the Republic of Korea (2014R1A1A2055295)).

Disclosure
This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (MEST) of the Republic of Korea (2014R1A1A2055295).

DOI: 10.1530/endoabs.37.GP.08.04

GP.08.05

Involvement of oestrogen receptor-α in λ-cyhalothrin and cypermethrin-induced cancer growth in BG-1 ovarian cancer cells expressing oestrogen receptor

Cho-Won Kim & Kyung-Chul Choi
Laboratory of Biochemistry and Immunology, College of Veterinary Medicine, Chungbuk National University, Cheongju, Chungbuk, Republic of Korea.

Synthetic pyrethroids (SPs) are the most common pesticides which are recently used for indoor pest control. The widespread use of SPs has resulted in the increased exposure to wild animals and humans. Recently, some SPs are suspected as endocrine disrupting chemicals (EDCs) and have been assessed for their potential oestrogenicity by adopting various analyzing assays. In this study, we examined the estrogenic effects of λ-cyhalothrin (LCT) and cypermethrin (CP), the most commonly used pesticides in Korea, in BG-1 ovarian cancer cells expressing estrogen receptors (ERs). To evaluate the estrogenic activities of two SPs, LCT and CP, we performed MTT assay and reverse-transcription polymerase chain reaction (RT-PCR) for LCT or CP treated BG-1 ovarian cancer cells. In MTT assay, LCT (10^{-6} M) and CP (10^{-5} M) significantly induced the growth of BG-1 cancer cells in a dose-dependent manner. LCT or CP-induced cell growth was reversed by addition of ICI 182 720 (10^{-8} M), an ER antagonist, suggesting that this effect appears to be mediated by an ER-dependent manner. Moreover, RT-PCR results showed that transcriptional level of ERα was significantly down-regulated by LCT and CP. Taken together, these results indicate that LCT and CP may possess estrogenic potentials to stimulate the growth of ovarian cancer cells expressing ERs via an ER-dependent manner. Based on the observations from these *in vitro* results, we will examine *in vivo* oestrogenicity of LCT and CP in a xenografted mouse model transplanted with human BG-1 ovarian cancer cells (This work was supported by Basic Science Research Program though the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (MEST) (2013R1A1A2059092)).

Disclosure
This work was supported by Basic Science Research Program though the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (MEST) (2013R1A1A2059092).

DOI: 10.1530/endoabs.37.GP.08.05

GP.08.06

Bisphenol A affects amelogenesis by modulating enamel key genes expression

Katia Jedeon[1,2], Sophia Houari[1,2], Blake Mcalpin[1,2], Sophia Loiodice[1,2], Ariane Berdal[1,2] & Sylvie Babajko[1,2]
[1]University Paris Diderot, Paris, France; [2]INSERM UMRS1138, Paris, France.

Bisphenol A (BPA) is a widespread endocrine disruptor commonly used by plastic industries. More than 95% of the world population contains BPA (ng/ml) in biological fluids raising the question of its activity and potential adverse effects. Anecdotally, molar incisor hypomineralisation (MIH), an

enamel pathology affecting 15–18% of children, is increasing concurrently with ED related pathologies. Our previous data show that BPA impacts amelogenesis and generate similar enamel defects as those described for MIH. The aim of the present study is to identify BPA target genes in order to characterize the mechanism of action of low-dose BPA in enamel hypomineralisation. First, rats were exposed daily to 5 μg/kg per day BPA from the conception to the sacrifice. RNAs from microdissected dental epithelia were submitted to microarray analysis. Among the 19 239 tested RNAs, only 41 were modulated (more than 1.5-fold) by BPA. Interestingly, among these genes, amelogenin and enamelin coding for specific enamel matrix proteins were ones of the highly up-regulated. Four other genes involved in mineralization process, SLC5A8, SLC26A4, SLC44A4 and Carbonic Anhydrase VB also appeared as BPA target genes which expression modulation may explain enamel hypomineralisation. Second, *in vitro* analysis carried out on the rat ameloblastic HAT7 cells also showed transcriptional modulations of enamel gene expression by 10^{-9} M BPA. Further studies are currently underway to decipher transcriptional modulations in relation with steroid receptors (ERα and AR) involved in BPA effects during amelogenesis. In conclusion, we report that BPA impacts enamel synthesis through modulations of enamel key gene expression. Despite the small number of BPA target genes specifically expressed in ameloblasts, ubiquitous receptors such as ERα and AR are involved in BPA effect transmission. Thus, these data help to understand how irreversible enamel defects may be used as early marker of exposure to BPA some years before the diagnosis of related heavy pathologies.

Disclosure
This work was supported by University Paris-Diderot, the French National Institute of Health and Medical Research (INSERM), Benjamin Delessert Institute (prix 2014) and French Institute for Odontological Research (IFRO).
DOI: 10.1530/endoabs.37.GP.08.06

GP.08.07

Cord blood insulin-like peptide 3 is reduced in idiopathic cryptorchidism and inversely related to free bisphenol A: a marker and/or an actor of foetal exposure to endocrine disruptors?

Patrick Fenichel[1,2], Najiba Lahlou[3], Nicolas Chevalier[1,2], Patrick Coquillard[4], Patricia Panaia-Ferrari[5], Kathy Wagner-Mahler[6], Michel Pugeat[7] & Francoise Brucker-Davis[1,2]
[1]Department of Endocrinology, Diabetology and Reproductive Medicine CHU de Nice, Nice, France; [2]Institut National de la Recherche Médicale, UMR U1065, Université Nice-Sophia Antipolis, Nice, France; [3]Department of Hormonology and Metabolic Disorders, Hôpital Cochin, APHP, Paris-Descartes University, Paris, France; [4]Institut Sophia-Agrobiotech [INRA-CNRS- Nice University], Sophia-Antipolis, France; [5]Department of Biochemistry, CHU Nice, Nice, France; [6]Department of Paediatrics, CHU Nice, Nice, France; [7]Fédération d'Endocrinologie, hospices civils de Lyon-1, Bron, France.

Introduction
Cryptorchidism, the most frequent congenital malformation in full-term male newborns, increases risk of infertility and testicular cancer. Most cases remain idiopathic but epidemiological and experimental studies have suggested the role of both genetic and environmental factors. Physiological testicular descent is regulated by two major Leydig cell hormones: Insulin-like peptide 3 (INSL3) and testosterone.
Methods and results
From a prospective case control study, 52 idiopathic non syndromic, cryptorchid newborns were compared to 118 matched controls, all born after 34 weeks pregnancy. Cord blood (cb) INSL3 (modified validated enzyme-linked immune-sorbent assay) but not cb testosterone (ultrapressure liquid chromatography-tandem mass spectrometry) was decreased in unilateral idiopathic cryptorchidism ($P=0.03$) especially in transient forms ($P=0.02$) and in the subgroup of non-palpable testis compared to the subgroup of palpable testes (supra-scrotal, inguinal or high scrotal) according to Scorer classification ($P=0.01$). cb free bisphenol A (BPA) (RIA validated by High Pressure Liquid Chromatography-tandem Mass Spectrometry) in cryptorchid boys was not significantly increased ($P=0.1$). However, in the whole study population (cryptorchid and control), cb free BPA correlated negatively with INSL3 ($P=0.01$; $R^2=0.05$) but not with testosterone.
Conclusion
INSL3, a major actor of foetal testicular descent, but not testosterone, is decreased at birth in idiopathic cryptorchidism. This hormonal decrease may have contributed earlier in foetal development, to the impaired testicular descend. The inverse correlation we found between cbINSL3 and cbBPA is strengthened by the paper reporting that INSL3 gene is negatively regulated by BPA in *ex vitro* cultivated foetal human testes. While measurements of cb BPA and cb INSL3 may not exactly reflect earlier foetal production or exposure, our results support the role of INSL3 as a marker and/or an actor of foetal exposure to endocrine disruptors such as BPA.

DOI: 10.1530/endoabs.37.GP.08.07

GP.08.08

Evidence of stimulation of pubertal development and suppression of growth rate in boys smoking marijuana in cigarettes

Shagufta Jabeen[1], Ghazala Kaukab Raja[1], Maleeha Akram[2], Afzal Ahmad[2], Mazhar Qayyum[2] & Shakeel Raza Rizvi[2]
[1]Department of Biochemistry Pir Mehr Ali Shah Arid Agriculture University Rawalpindi, Rawalpindi, Pakistan; [2]Department of Zoology Pir Mehr Ali Shah Arid Agriculture University Rawalpindi, Rawalpindi, Pakistan.

Evidence indicates that normal pattern of progression of puberty is altered under certain conditions of stress, whereas growth rate is affected by sustained higher concentrations of cortisol, a marker of stress reactivity. Available data show that early teens commonly resort to use of drugs. The use of drugs may evoke stress responses, which may alter pubertal development and affect growth rate. Body weight (BW), height, BMI and plasma concentrations of LH, testosterone (T), GH and cortisol were determined in non-smoking ($n=220$) and marijuana addicted ($n=217$) boys. Acute effect of marijuana on salivary concentrations of cortisol was assessed by giving 0.25 g of marijuana in cigarettes to ten drug addict volunteers and determining salivary cortisol concentrations 15 min before and 1, 5, 15 and 30 min after smoking. Data were analysed using Student's *t*-test, ANOVA and Pearson correlation. Mean BW, height, BMI and plasma LH, T and cortisol concentrations increased throughout puberty, whereas plasma concentrations of GH attaining peak concentrations at mid puberty declined during late puberty/adolescence in both groups. Although circulating concentrations of LH, T and cortisol showed positive correlation throughout puberty, plasma GH concentrations were negatively correlated with LH, T and cortisol at late puberty/adolescence in both groups. The plasma concentrations of LH, T and cortisol were significantly higher in addict boys, whereas plasma GH concentrations were significantly higher in non-smoking boys during puberty. The higher levels of LH and T exhibited a positive relationship with marijuana use in addict boys. The non-smoking boys were 4 kg heavier and 4.6 inches taller than addict boys at the age of 20 years. Acute administration of marijuana induced significant increases in the salivary concentrations of cortisol. In conclusion, marijuana use may provoke stress responses resulting in stimulation of pubertal development and suppression of growth rate.

DOI: 10.1530/endoabs.37.GP.08.08

Nuclear receptors and signalling

GP.09.01

Comparison of mRNA expression pattern of retinoid and retinoid X nuclear receptor subtypes in thyroid carcinomas, breast cancer and renal carcinomas

Julius Brtko[1], Lucia Bialesova[1], Vladimir Lenko[1,3], Stefan Galbavy[2], Jan Podoba[2] & Dana Macejova[1]
[1]Institute of Experimental Endocrinology, Slovak Academy of Sciences, Bratislava, Slovakia; [2]Saint Elizabeth Institute of Oncology, Bratislava, Slovakia; [3]University Hospital, Bratislava, Slovakia.

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

three different organ malignancies, i) thyroid different carcinoma tissues, ii) breast cancer, and iii) renal cancer tissues.
Description of methods/design
Approximately 40 samples of different types of thyroid carcinoma, more than 150 breast cancer samples, and over 100 samples of renal carcinoma have been analyzed. The expression pattern of the retinoid/rexinoid nuclear receptor subtypes has been evaluated by the RT-PCR techniques.
Results
Significantly increased expression of RARα and RARγ in overall group of papillary carcinoma patients was demonstrated. In breast cancer, the expression of respective RAR subtypes was in the following order: RARα >RARβ >RARγ. Among RXR subtypes, only RXRγ was significantly diminished in breast cancer tissue. In renal carcinomas, expression of RARα and RARβ was higher when compared to intact kidney tissue. Expression of RARγ was found to be markedly decreased in all renal tumours. All renal tumours were capable to express RXRα and RXRβ. Expression of RXRγ was significantly lower in comparison with intact renal tissue.
Conclusion
The molecular mechanisms demonstrating differences in RAR and RXR subtype mRNA expression patterns in thyroid carcinomas, breast and renal cancer may find exploitation in clinical oncology, predominantly, in the differential diagnosis of different organ neoplasms.
Disclosure
Supported by the grant APVV-0160-11, the VEGA grant 2/0171/14, and the Centre of Excellence CEMAN grant.
DOI: 10.1530/endoabs.37.GP.09.01

GP.09.02

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

Livio Casarini[1,2] & Manuela Simoni[1,3]
[1]Unit of Endocrinology, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy; [2]Center for Genome Research, University of Modena and Reggio Emilia, Modena, Italy; [3]Azienda USL of Modena, Modena, Italy.

Background
The immortalised human granulosa cell line (hGL5) is not responding to gonadotropins, which fail to activate the cAMP/PKA/CREB pathway, progesterone production, cell rounding and apoptosis, suggesting that FSH- and LH/hCG-receptors (FSHR; LHCGR) are downregulated.
Aim
To investigate whether the mechanism of FSHR/LHCGR downregulation is associated with life/death signals in hGL5 cells.
Methods
We evaluated the FSHR/LHCGR expression in cultured hGL5 cells (0–15% serum) by real-time PCR and western blotting. The response to 50 nM FSH or 100 pM LH was evaluated by measuring cAMP and progesterone production by ELISA, as well as ERK1/2 and CREB phosphorylation by western blotting, cell viability by proliferation assay and confocal imaging, in the presence or absence of selective inhibitors/agonists (i.e. the PKA inhibitor H-89, PMA as a PKC-ERK1/2 activator, siRNA against β-arrestin1/2).
Results
Despite the positive expression of FSHR/LHCGR in the presence of serum at both mRNA and protein level (linear regression; $P<0.05$; $n=3$), FSH/LH stimulation was ineffective on cAMP/pCREB activation and progesterone production (Mann-Whitney's *U*-test; $P\geq0.05$; $n=3$), suggesting uncoupling of the receptors to the Gs-α protein. Conversely, ERK1/2 phosphorylation was FSH/LH- and dose-dependent in the presence of serum, increasing cell proliferation within 3 days, an effect similar to that obtained by PMA (Mann-Whitney's *U*-test; $P<0.05$; $n=3$). β-arrestin1/2 siRNA transfection unlocked the cAMP/PKA pathway, leading to cAMP/CREB activation and progesterone accumulation at high levels (Mann-Whitney's *U*-test; $P<0.05$; $n=3$), cell rounding, pro-caspase three cleavage and apoptosis. The pro-apoptotic effects of cAMP/PKA basal activation were augmented by FSH -but not LH- treatment and inhibited by H-89 selective PKA blockade. Accordingly, long-term (4–8 weeks) overexpression of FSHR resulted in high basal cAMP levels, cell rounding and apoptosis (Mann-Whitney's *U*-test; $P<0.05$; $n=3$), revealing the peculiar, dual role of FSHR in the activation of proliferative/apoptotic signals.
Conclusions
β-arrestins determine the FSHR-, rather than LHCGR-mediated signalling towards proliferative/apoptotic pathways, acting as selective switch between ERK or cAMP/PKA pathway activation.
Disclosure
This work was supported by a grant of the Italian Ministry of Education, University and Research (PRIN 2010C8ERKX).
DOI: 10.1530/endoabs.37.GP.09.02

GP.09.03

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

Andreas Lehmann, Stefan Schulz & Thomas Günther
Institute of Pharmacology and Toxicology, University Hospital Jena, Jena, Germany.

The human somatostatin receptor 3 (hsst3) is expressed in about 50% of all neuroendocrine tumours. The sst3 receptor is unique among somatostatin receptors which can initiate apoptosis of tumour cells through activation of the tumour suppressor p53. Furthermore, treatment of the sst3 receptor with somatostatin or stable somatostatin analogues such as octreotide or pasireotide can inhibited tumour cell proliferation. However, at present little is known about the agonist-induced regulation of the human sst3 receptor. We have generated a series of phosphorylation-deficient mutants of the receptor and determined important sites for agonist-induced internalisation. Based on this information we generated phosphosite-specific antibodies for the carboxyl-terminal serine 337, threonine 341 and threonine 348, which enabled us to investigate the temporal patterns of sst3 phosphorylation and dephosphorylation. Here we demonstrate that pasireotide and octreotide were not able to promote a phosphorylation to the same extent as natural somatostatin. Similar the sst3-selective ligand L-796,778 did not promote any detectable phosphorylation or internalisation. We also show that sst3 phosphorylation occurred within minutes, whereas dephosphorylation and recycling of the sst3 receptor occurred at a considerably slower rat. We also identify G protein-coupled receptor kinases 2 and 3 (GRK2/3) and protein phosphatase 1 (PP1) as key regulators of sst3 phosphorylation and dephosphorylation.
DOI: 10.1530/endoabs.37.GP.09.03

GP.09.04

Characterisation of insulin and β_2-adrenergic receptor heteromers: experimental and bioinformatics approach

Maja Mandić[1], Sanja Glisic[2], Christina Pedersen[3], Nevena Veljkovic[2], Jane Nøhr[3] & Milka Vrecl[1]
[1]Veterinary Faculty, Institute of Anatomy, Histology and Embryology, University of Ljubljana, Ljubljana, Slovenia; [2]Institute of Nuclear Sciences VINCA, Center for Multidisciplinary Research, University of Belgrade, Belgrade, Serbia; [3]Department of Incretin Biology, Novo Nordisk A/S, Måløv, Denmark.

Evidences for a functional link between insulin receptor (IR) and β_2-adrenergic receptor (β_2AR) exist in the mouse heart and in retina and are correlated with the cardiovascular dysfunction under insulin-resistant states[1] and a diabetic retinopathy phenotype[2]. In our recent study we showed that i) IR coexpression reduced β_2AR surface expression and accelerated its internalization, ii) provided evidence for direct interaction and higher-order β_2AR:IR oligomer formation, likely comprising heteromers of homodimers, and iii) identified prospective intracellular interaction domains engaged in heteromerisation[3]. In this study we examined the involvement of the cytoplasmic part of the IR β chain in heteromerisation and addressed the role of β_2AR:IR heteromer in signalling. Evidence suggesting that the cytoplasmic part of the IR β chain is prerequisite for the interaction with the β_2AR was provided by BRET[2] saturation and Heteromer Identification Technology (HIT) assays using a IR 1–1271 mutant lacking the IR C-terminal tail region (amino acids from 1272 to 1360). In BRET[2] saturation assays, IR 1–1271–Rluc8 mutant displayed lower $BRET_{max}$ value and slightly reduced affinity compared to the WT IR. For the complex consisting of IR 1–1271–RLuc8:β_2AR-GFP[2] the saturation was not reached; most likely reflecting only random collisions. Furthermore, in the IR 1–1271–Rluc8:β_2AR HIT assay with β-arrestin 2 no substantial agonist-induced increase in BRET[2] signal was detected that would be indicative of β-arrestin 2 recruitment to the IR 1–1271–Rluc8:β_2AR heteromer, arguing against ability of IR 1–1271 to heteromerise with the β_2AR. Additional *in silico* mutation analysis of IR predicted substitutions mostly affecting the binding to the β_2AR. β_2AR:IR heteromerization also influenced the pharmacological phenotype of the β_2AR i.e. its ability to recruit β-arrestin 2 and cAMP signalling.

References
1. Fu Q, Xu B, Liu Y, Parikh D, Li J, *et al*. *Diabetes* 2013 **63** 2676–2689.
2. Jiang Y, Zhang Q, Liu L, Tang J, Kern TS & Steinle JJ. *PLoS One* 2013 **8** (7) e70555.
3. Mandić M, Drinovec L, Glisic S, Veljkovic N, Nøhr J & Vrecl M. *PLoS One* 2014 **9** (11) e112664.
Disclosure
We acknowledge funding from the Basileus program to M Mandic, Slovenian Research Agency program P4-0053 to M Vrecl and the Ministry of Education, Science and Technological Development of the Republic of Serbia (grant number 173001) to S Glisic.
DOI: 10.1530/endoabs.37.GP.09.04

GP.09.05

Neuroprotective effects of 17β-oestradiol: a therapeutic potential drug for Alzheimer's disease

Pardeep Kumar, R K Kale & N Z Baquer
Jawaharlal Nehru University, New Delhi, India.

Objectives
Alzheimer's disease (AD) is the most common form of dementia in the elderly. AD is characterized by the presence of amyloid plaques which are formed from deposits of β-amyloid protein (Ab). These changes increase during menopausal condition in females when the level of oestradiol (E_2) is decreased. The aim of the present study was to determine the effect of neuropeptide, neurokinin B (NKB) and amyloid beta fragment Aβ (25–35) on E_2 treated aging female rat brain of 3 months (young), 12 months (adult), and 24 months (old) age groups.
Methods
The aged rats (12 and 24 months old) ($n=8$ for each group) were given s.c. injection of E_2 (0.1 μg/g body weight) daily for 1 month. After 30 days of hormone treatment, experimental animals of all the groups were sacrificed and brains were isolated for further study.
Results
The results obtained in the present work revealed that increased activities of antioxidant enzymes, membrane bound ATPases and decrease in level of calcium levels, monoamine oxidase activity and lipid peroxidation in presence of NKB and combined NKB and Aβ *in vivo* E_2 treated ageing rat brain. NKB treatment reversed the beneficial in preventing some of the age related changes in the brain. An *in vitro* incubation of E_2 treated synaptosomes with Aβ showed toxic effects on all the parameters, while NKB showed stimulating effects and the combined NKB and Aβ showed a partial effects as compared to Aβ (25–35) and NKB alone.
Conclusions
Present study elucidates an antioxidant, neuromodulatory and neuroprotective role of tachykinin peptide NKB against the β-amyloid induced toxicity in E_2 treated female rats. NKB treatment reversed the beneficial in preventing some of the age related changes in the brain.
Disclosure
CSIR grant 2005–6.
DOI: 10.1530/endoabs.37.GP.09.05

GP.09.06

Effects of estrogens on endothelial-derived factors implicated in the atheromatic plaque vulnerability-clarification of the molecular mechanisms

Narjes Nasiri Ansari[1], Eliana Spilioti[1], Vasiliki Kalotychou[2], Karin Dalman-Wright[3], Paraskevi Moutsatsou[1], Athanasios Papavassiliou[1] & Eva Kassi[1]
[1]Laboratory of Biochemistry, Medical School, National and Kapodistrian University of Athens, Athens, Greece; [2]1st Department of Internal Medicine, Medical School, National and Kapodistrian University of Athens, Athens, Greece; [3]Department of Biosciences and Nutrition, Karolinska Institute, Stockholm, Sweden.

Introduction
In the presence of atherogenic plaque, estrogens may be potentially harmful. Among the key vessel wall components in the later stages of atherogenic process are endothelial cells (ECs). During the stages of plaque instability/rupture, metalloproteinases (MMP2 and MMP9), their inhibitors (TIMP2 and TIMP1), RANK, RANKL, OPG, MCP1, lysyl oxidase (LOX), PDGF, and ADAMTS4 play critical role. We aimed to investigate i) the effect of oestrogens on the expression of the above molecules in ECs and ii) which type of estrogen receptor mediates these effects.
Methods
Human aortic endothelial cells (HAECs) were cultured, in the absence or in the presence of estradiol (E_2) at various concentrations and for various incubation times without or with pre-incubation with TNFα (resembling a low grade inflammation state). The mRNA expression of all the aforementioned genes was assessed by real-time PCR. Zymography for MMP2 and MMP9 activity was also performed. The experiments were repeated in either ERα- or ERβ-transfected HAECs.
Results
HAECs did not express ERα and ERβ while they express G-protein coupled estrogen receptor 30 (GPR30). Incubation with E_2 at low concentrations induced an increase in LOX and MCP1 mRNA expression. Zymography revealed that E_2 induced a down regulation of active MMP2, dose-dependently. Incubation with E_2 following pretreatment with TNFα induced a marginal increase in MMP9 and TIMP1 expression and a ten times increase in MCP1, dose-dependently. In ERα-transfected HAECs, incubation with E_2 led to upregulation of TIMP1 and TIMP2 and in marginal increase of LOX and MCP1. E_2 increased the expression of MCP1 and LOX while decreased the expression of PDGF in ERβ-transfected HAECs.
Conclusion
E_2 induced different effects regarding atherogenic plaque instability through different ERs. The balance of expression of the various ER subtypes may play an important role in the paradoxical characterization of estrogens as both beneficial and harmful.
Disclosure
General Secretariat for Research and Technology.
DOI: 10.1530/endoabs.37.GP.09.06

GP.09.07

Androgen modulates expression of energy-related genes in brown adipocytes

Avi Lerner, Drashti Kewada, Anthony Okolo, Kate Hardy & Stephen Franks
Imperial College London, London, UK.

Polycystic ovary syndrome (PCOS) is a common endocrinopathy is associated with an adverse metabolic profile including obesity, insulin resistance, and dyslipidaemia. Hyperandrogenism is the hallmark of PCOS and androgen production is increased in the presence of increased adiposity. While a clear link between obesity and the severity of PCOS exists, the relationship between hyperandrogenism and adipose tissue is less clear. Interestingly, women with PCOS and raised androgen levels exhibit reduced postprandial thermogenesis (Robinson *et al*. *J Clin Endocrinol* 1992 **36** 537). Brown adipose tissue (BAT) is important in non-shivering and postprandial thermogenesis. In this study, we investigated the effect of androgen treatment on the differentiation and gene expression of BAT. Immortalised mouse brown preadipocytes were differentiated for 14 days in the presence and absence of dihydrotestosterone (DHT). In addition, fully differentiated adipocytes were treated with DHT or control for 24 h. Adipogenesis was observed using Oil Red O staining and quantitative PCR was used to analyse differential gene expression for a panel of genes. Our results show that DHT treatment inhibits brown fat adipogenesis in a dose-dependent manner. Hyperandrogenism also causes dysregulation of normal gene expression and several markers for BAT and thermogenesis were significantly perturbed. These included downregulation of the adipokine desnutrin/ATGL (a key gene required for BAT identity and thermogenesis) ($P<0.01$) and C/EBPα (an important early regulator of brown adipose markers and normal energy metabolism) ($P<0.01$). Furthermore, DHT treatment caused distinctive adipokine profiles similar to those found in metabolic syndrome and insulin resistance such as reduced adiponectin ($P<0.05$) and raised PAI-1 ($P<0.05$). These results suggest that androgens play a role in brown adipocyte differentiation and function and lend support for a reciprocal relationship between androgens, BAT and thermogenesis.
Disclosure
MRC Program grant (P22061).
DOI: 10.1530/endoabs.37.GP.09.07

GP.09.08

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

Magalie Haissaguerre[1,2], Samantha Clark[1,2], Antoine Tabarin[1,3] & Daniela Cota[1,2]
[1]INSERM U862, Neurocentre Magendie, Bordeaux, France; [2]University of Bordeaux, Bordeaux, France; [3]Endocrinology Department, Haut Leveque Hospital, University Hospital of Bordeaux, Pessac, France.

Obesity and its consequent metabolic disorders are severe health problems. The mechanistic target of rapamycin complex 1 (mTORC1) pathway is an important hypothalamic integrator of the actions of nutrients and hormones on food intake (FI). Nutrient availability also affects the formation of reactive oxygen species (ROS) in the hypothalamus and regulates neuronal activity. In the present study, we hypothesise that modulation of mTORC1 activity mediates ROS effects on FI. To this purpose, C57Bl6J mice or WT and KO mice deficient for the mTORC1 downstream target S6K1 were treated with an i.c.v. injection of the ROS producer H_2O_2 or the ROS scavenger honokiol, alone or in combination with the mTOR inhibitor rapamycin or the mTOR activator leptin and changes in FI and body weight were assessed. Western blots were performed to study hypothalamic mTORC1 activity. ROS levels were analysed in POMC neurons using dihydroethidium combined with immunofluorescence. I.c.v. administration of H_2O_2 induced phosphorylation of S6K1 within the hypothalamus, increased expression of c-fos, a marker of neuronal activity, in the arcuate nucleus and increased ROS signal in POMC neurons. These effects were associated with a significant decrease in food intake over 24 h. Conversely, i.c.v. administration of honokiol increased FI. The behavioural effects of H_2O_2 and honokiol were not seen in S6K1 KO mice. Pharmacological experiments using i.c.v. coadministration of H_2O_2 and rapamycin in C57Bl6J mice showed that rapamycin (at a dose not acting on FI) was able to blunt the anorexigenic effect of H_2O_2. Similarly, i.c.v. honokiol administration combined with an i.p. leptin injection decreased the anorexigenic effect of leptin, suggesting that leptin requires ROS formation to reduce FI. Our preliminary results confirm that ROS modulators require a functional mTORC1 pathway to regulate FI. Studies are ongoing to better define this relationship at the molecular and neuroanatomical level.

DOI: 10.1530/endoabs.37.GP.09.08

Calcium, Vitamin D and Bone

GP.10.01

Roles of membrane oestrogen receptor alpha in bone sparing effects of oestrogens

Alexia Vinel[1], Coralie Fontaine[1], Eric Hay[2], Marie Valera[1], Françoise Lenfant[1], Martine Cohen-Solal[2] & Jean-François Arnal[1]
[1]INSERM U1048, Université Paul Sabatier, Toulouse, France; [2]INSERM UMR-1132, Université Paris Diderot, Sorbonne, Paris, France.

Introduction
The bone-sparing effect of oestrogen is mediated via oestrogen receptor alpha (ERα), which stimulates transcriptional action through its two activation functions (AF1 and AF2). In addition to these nuclear effects, a fraction of this receptor is targeted to the plasma membrane and triggers membrane initiated steroid signaling (MISS). Whereas, ERα AF1 plays a crucial role in trabecular bone, but not cortical bone, ERα AF2 is necessary for the oestrogen effect in both types of bone. A pharmacological approach using an oestrogen dendrimer conjugate suggested that the selective activation of membrane ERα is sufficient to elicit a sparing effect in cortical but not in trabecular bone.
Methods
The aim of this study was to define the role of ERαMISS on the beneficial actions of oestrogens on bone *in vivo*, using a mouse model in which ERα membrane localisation is abrogated due to a point mutation of the palmitoylation site of ERα (C451A-ERα).
Results
Intact (unovariectomised) C451A-ERα mice showed an accelerated loss of both trabecular and cortical bone compared to littermate WT controls. Furthermore, chronic 17β-oestradiol administration (8 μg/kg per day) elicited a strong bone protection in ovariectomised mice, whereas, these actions were significantly reduced in C451A-ERα mice.
Conclusion
We show here that in bone tissues, membrane ERα is necessary for oestrogen protection and thus that nuclear and membrane actions cooperate to the bone sparing effects of oestrogens. This contrasts with the absence of ERαMISS role for the uterotrophic action of oestrogens. Our work underlines the exquisite tissue-specific actions of ERα subfunctions, and should help to understand the mechanisms by which selective ER modulators can act *in vivo*.

DOI: 10.1530/endoabs.37.GP.10.01

GP.10.02

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

Martin Kužma[1], Eva Némethová[2], Zdenko Killinger[1] & Juraj Payer[1]
[1]5th Department of Internal Medicine, Faculty of Medicine, Comenius University and University Hospital, Bratislava, Slovakia; [2]Department of Internal Medicine, Dunajská Streda Hospital, Dunajská Streda, Slovakia.

Introduction
More than half of osteopenic patients suffer from fracture (Fx), but BMD osteopenia is usually not considered for treatment initiation. FRAX, tool that can identify patients with high Fx risk based on major risk factors, can be used as an interventional threshold. Past few years, trabecular bone score (TBS), the bone quality determinant, is a promising method identifying the high-risk patients according to degradation of trabecular bone.
Objective
Comparison of two methods, TBS and FRAX, in treatment consideration between postmenopausal women with osteopenia.
Methods
The group of osteopenic postmenopausal women were retrospectively analyzed. Using NOF cutoff values of 20% for major osteoporotic fracture and 3% for hip fracture were used to consider patients at high absolute 10 years risk of Fx. According to temporary consensus guidelines patients with BMD osteopenia+ very low (degraded) TBS (<1.1) should be treated after secondary cause was excluded. TBS Insight tool was used to assess TBS derived from L-spine DXA scans.
Results
157 postmenopausal women (mean age 65.9 years, BMI 26.7 kg/m^2, *T*-score: neck -1.2; L-spine 1.4, and TBS 1.24) were included. In total, by NOF cutoff 44 (28%) patients, who may be treated were identified. From that number 20 (12.7%) patients belonged to highly degraded TBS group. Another 32 (20.3%) patients with highly degraded TBS were identified in low risk FRAX group.
Conclusion
In the present study, the FRAX tool was able to identify additional 28% more patients in high fracture risk, which should be considered for treatment. From NOF high-risk group TBS identified 20 patients at increased risk of fracture and additional 32 patients from whole study group with degraded TBS who should be treated. According to this study, addition of TBS to FRAX brings novel info in identifying high Fx risk patients with osteopenia.

DOI: 10.1530/endoabs.37.GP.10.02

GP.10.03

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

Luke Watson[2], Xi Zhe Chen[1], Aideen Ryan[1], Paul Loftus[2], Patrick McDonnell[1], Timothy O'Brien[1] & Cynthia Coleman[1]
[1]National University of Ireland Galway, Galway, Ireland; [2]Orbsen Therapeutics, Galway, Ireland.

Fractures in diabetic patients are slower to heal and have an increased risk for developing malunion as compared to non-diabetic individuals. Given the known deficiencies in diabetic progenitor cell number and differentiation capacity, it is reasonable to hypothesise the aetiology of diabetic fracture malunion is dysregulated progenitor function. Therefore, we investigated the therapeutic efficacy of locally administered non-diabetic human bone marrow derived mesenchymal stem cells (hMSCs) to support femoral fracture repair in a murine model of diabetes.
A dose escalation study was performed administering hMSCs directly to a femoral fracture in a murine model of diabetes. The effect of local hMSC administration on the diabetic condition was evaluated by weekly monitoring of mouse weight, blood glucose, and terminal levels of circulating HbA1c. No significant change in body weight, blood glucose, or HbA1c as a result of hMSC administration was observed throughout the 56-day study. Animals maintained their weight at 26–28 g, their blood glucose levels >13 mM and HbA1c levels of 10–15% regardless of treatment group. MicroCT analysis indicates an increase in bone volume, a statistically significant increase in bone mineral density and trabecular thickness and a statistically significant decrease in the ratio of bone surface area to bone volume in animals treated with hMSCs as compared to saline treated controls. Further, four point bending analysis demonstrated a statistically significant increase in ultimate stress and e-modulus of the reparative bone. Although, the local administration of hMSCs did not alter the organismal diabetic condition, treatment of the diabetic fracture with hMSCs resulted in enhanced mechanical integrity of de novo reparative bone.

Therefore, the local administration of non-diabetic hMSCs to diabetic fractures has the potential to enhance callus remodelling resulting in the deposition of higher quality reparative bone.

Disclosure
This work was supported by European Union Framework 7 Program HEALTH-F2-2012-305736.

DOI: 10.1530/endoabs.37.GP.10.03

GP.10.04

Osteoporosis and osteopenia in patients after kidney and pancreas transplantation

Jana Brunova[1], Simona Kratochvilova[1] & Josef Bruna[2]
[1]Institute for Clinical and Experimental Medicine, Prague, Czech Republic; [2]Medical Faculty Hospital Motol, Prague, Czech Republic.

Background
Organ transplantation (Tx) is the standard treatment for end-stage renal failure in diabetic patients. With an improvement in patient and graft survival, the bone loss and persistent abnormalities in bone metabolism are long-term complications to manage.
Patients and methods
We investigated the prevalence of osteoporosis and osteopenia in 256 diabetic patients (142M, 114F) after the kidney and pancreas Tx for renal failure due to diabetic nephropathy. The bone loss was diagnosed with densitometry (DEXA) using Lunar Prodigy apparatus in years 2010–2014. The characteristics of bone metabolism were regularly examined and we measured on the plain CXR the clavicle bone index, which is the ratio of cortical bone width to total bone width at the midpoint of the shaft.
Results
Osteoporosis of lumbar spine (L spine) and/or hips was diagnosed in 53/256 patients (20%), osteopenia in 135/256 (52%) and 68/256 (28%) of patients had normal bone density. Patients with osteoporosis had affected mainly proximal femurs (hips) in (50/53 (94%) cases and distal forearm in 32/53 (60%). Osteoporosis of L spine was proven in 11/53 patients (21%) and osteopenia in 28/53 (53%) cases. Patients did not differ significantly in age, creatinine, calcium and parathormone (PTH) level. There was a tendency to lower BMD with years after the kidney and pancreas Tx (see Table). The bone index showed good correlation with the bone density measured by DEXA ($P<0.01$).

Patients	*n*	Age (years)	After Tx (years)	Creatinine (μmol/l)	Ca (mmol/l)	PTH (pmol/l)
Osteoporosis	53	51.7	8.4	147.7	2.4	14.6
Osteopenia	135	52.9	7.7	145.3	2.4	16.7
Normal BMD	68	54.6	6.8	147.3	2.4	13.8

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

DOI: 10.1530/endoabs.37.GP.10.04

GP.10.05

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

Mariska Vlot, Maartje Klaver, Paul Lips, Renate de Jongh, Annemieke Heijboer & Martin den Heijer
VU Medical Center, Amsterdam, The Netherlands.

Background
Oestrogen can increase bone mineral density (BMD) by decreasing bone turnover, which is mainly seen in trabecular bone. Testosterone can increase bone size, but the effect on BMD is less clear. Cross-sex hormonal treatment (CSHT) in transsexuals can therefore affect the BMD. For example, in male-to-female individuals (MtFs) a lower BMD before start of CSHT has been described in comparison to healthy control men.
Objectives
To investigate the effects of CSHT on BMD during the first year of hormonal treatment in MtFs and female-to-male individuals (FtMs).
Methods
Prospective study, part of European Network for Investigation of Gender Incongruence (ENIGI). 74 adult patients who completed 1 year of CSHT were included. In 37 FtMs and 37 MtFs a dual-energy X-ray absorptiometry (DEXA) was performed to measure the BMD of the spine at start and after a year of CSHT. The FtMs received testosterone undecanoate i.m. (1000 mg/12 weeks), testosterone gel (50 mg/day), or testosterone esters i.m. (250 mg/2 weeks). The MtF group was treated with estradiol valerate (2–4 mg/day) or an estradiol patch (200 μg/week) and most MtFs received cyproteronacetate (50 mg/day) simultaneously.
Results
At baseline the BMD of the spine of the FtMs was 0.99 g/cm^2 (S.D. $\pm$0.10) and after 1 year 1.00 g/cm^2 (S.D. $\pm$0.10) reflecting a mean difference of 1% (95% CI $-$0.31 to 2.24). In the MtFs at baseline and after 1 year, the BMD of the spine was 1.00 g/cm^2, (S.D. $\pm$0.11) and 1.03 g/cm^2 (S.D. $\pm$0.11) respectively, reflecting a mean difference of 3.6% (95% CI 2.30 to 4.86).
Conclusion
In FtMs the BMD of the spine remained stable after 1 year CSHT. In the MtFs group, the BMD increased on average with 3%. Taken into account the short study period, the change in BMD suggests that BMD is an important variable in the follow up of transsexuals.

DOI: 10.1530/endoabs.37.GP.10.05

GP.10.06

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

Anastasia Markatseli[1], Leandros Lazaros[2], Harilaos Kostoulas[2], Sofia Markoula[2], Stelios Tigas[1], Ioannis Georgiou[2] & Agathocles Tsatsoulis[1]
[1]Department of Endocrinology, University of Ioannina, Ioannina, Greece; [2]Laboratory of Human Reproductive Genetics, Department of Obstetrics and Gynecology, University of Ioannina, Ioannina, Greece.

Introduction
Osteoporosis is a systemic skeletal disease with a strong genetic component. The androgen receptor (AR) is encoded by the *AR* gene and mediates the action of androgens, which play an important role in bone metabolism. Polymorphisms in the *AR* gene may be implicated in the pathogenesis of osteoporosis.
Objectives
The present study aimed to explore the influence of the (*CAG*)*n* repeat polymorphism of *AR* gene on BMD and serum levels of osteoprotegerin (OPG), receptor activator of nuclear factor-κB ligand (RANKL), and bone metabolic markers in a Greek female population.
Methods
Two hundred and seventeen peri- and postmenopausal women aged 42–63 years were enrolled. All participants underwent spinal BMD evaluation by dual-energy X-ray absorptiometry (DXA). Genotyping of the (*CAG*)*n* repeat polymorphism was performed by PCR. Levels of OPG, soluble RANKL (sRANKL), and bone metabolic markers were measured.
Results
Genotype analysis revealed alleles having 15–30 CAG repeats. The (*CAG*)*n* polymorphism was significantly associated with spinal BMD. Women having biallelic mean CAG repeat number $\geq$21 had significantly lower spinal BMD (0.797 ± 0.107 g/cm^2) than women having biallelic mean CAG repeat number $<$21 (0.841 ± 0.129 g/cm^2) ($P=0.007$). The association remained significant after adjustment for age, years since menopause (YSM) and BMI ($P=0.016$). Additionally, calcium concentration in serum was associated with the (*CAG*)*n* polymorphism. Calcium concentration in serum was higher in women with biallelic mean CAG repeat number $\geq$21 (9.88 ± 0.48 mg/dl) than in women with biallelic mean CAG repeat number $<$21 (9.73 ± 0.44 mg/dl) ($P=0.017$). No effect was observed on circulating levels of OPG and sRANKL.
Conclusions
The (*CAG*)*n* polymorphism of the *AR* gene may influence BMD at the lumbar spine in menopausal Greek women.

DOI: 10.1530/endoabs.37.GP.10.06

GP.10.07

Abstract withdrawn.

DOI: 10.1530/endoabs.37.GP.10.07

GP.10.08

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

Alberto Ferlin, Riccardo Selice, Antonella Di Mambro, Marco Ghezzi, Nicola Caretta & Carlo Foresta
Department of Medicine, University of Padova, Padova, Italy.

Introduction
Decreased bone mineral density (BMD) in Klinefelter syndrome (KS) is frequent and it has been traditionally related to low testosterone levels. However, low BMD can be observed also in patients with normal testosterone levels and testosterone replacement therapy does not necessarily increase bone mass in these patients. Nothing is known about vitamin D levels and supplementation in KS. In this study we determine vitamin D status and bone mass in KS subjects and compare the efficacy of testosterone therapy and vitamin D supplementation on BMD.
Methods
A total of 127 non-mosaic KS patients and 60 age-matched male controls were evaluated with reproductive hormones, 25-hydroxyvitamin D, PTH, and bone densitometry by DEXA. Patients with hypogonadism and/or 25-hydroxyvitamin D deficiency were treated with testosterone-gel 2% and/or calcifediol and re-evaluated after 24 months of treatment.
Results
25-hydroxyvitamin D levels were significantly lower in KS patients with respect to controls, and they had significantly lower lumbar and femoral BMD. The percentage of osteopenia/osteoporosis in subjects with 25-hydroxyvitamin D deficiency was higher with respect to subjects with normal 25-hydroxyvitamin D and was not related to the presence/absence of low testosterone levels. Subjects treated with calcifediol or testosterone + calcifediol had a significant increase in lumbar BMD after treatment. No difference was found in testosterone-treated group.
Conclusions
These data highlight that low 25-hydroxyvitamin D levels have a more critical role than low testosterone levels in inducing low BMD in KS subjects. Furthermore, vitamin D supplementation seems to be more effective than testosterone replacement therapy alone in increasing BMD.

DOI: 10.1530/endoabs.37.GP.10.08

GP.10.09

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

Chiara Verdelli[1], Federica Ermetici[2], Marcello Filopanti[3], Uberta Verga[3], Elena Passeri[4], Giorgia Dito[4], Alexis Elias Malavazos[2], C Mapelli[5], M E Raggi[5] & Sabrina Corbetta[4]
[1]Laboratory of Molecular Biology, IRCCS Policlinico San Donato, San Donato Milanese (MI), Italy; [2]Diabetology and Metabolic Diseases Unit, IRCCS Policlinico San Donato, San Donato Milanese (MI), Italy; [3]Endocrine and Diabetology Unit, IRCCS Fondazione Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; [4]Endocrinology and Diabetology Unit, Department of Biomedical Sciences for Health, University of Milan, IRCCS Policlinico San Donato, San Donato Milanese (MI), Italy; [5]Clinical Pathology Laboratory, IRCCS E. Medea, Bosisio Parini (LC), Italy.

Patients with primary hyperparathyroidism (PHPT) are at risk of chronic kidney disease (CKD). PHPT patients ($n=190$, 146 females and 44 males, aged 59.7 ± 14.2 years) and non-hypertensive, non-diabetic age- and sex-matched healthy controls were evaluated for serum cystatin C and creatinine. PHPT patients and controls with established CKD were excluded. Serum cystatin C was measured by immunonephelometric assay and calculation of estimated glomerular filtration rate (eGFR) was based on serum creatinine and cystatin C (eGFRcr-cys) using the CKD–EPI equation. Serum cystatin C well correlated with serum creatinine in PHPT patients ($r=0.594$, $P=0.0001$), while mean cystatin C level was significantly higher in PHPT patients than in healthy controls (0.93 ± 0.02 mg/l vs 0.78 ± 0.01 mg/l, $P=0.001$). In particular, among PHPT patients with eGFRcr >60 ml/min per 1.73 m^2, 18.4% had cystatin C levels >1.03 mg/l (95th percentile of controls' values), consistent with a 'preclinical kidney disease'. These patients had higher HOMA-IR values and were more hypertensive. In PHPT patients, cystatin C levels positively correlated with total and ionized calcium ($r=0.151$, $P=0.024$ and $r=0.259$, $P=0.004$) and with PTH ($r=0.176$, $P=0.01$). Using the eGFRcr-cys equation, CKD (stages G3a, 3b, and 4) was diagnosed in 13.7% of PHPT patients. CKD–PHPT patients had higher total and ionized calcium, were older, more frequently males, heavier, more insulin-resistant and more frequently affected with hypertension. Any significant correlation with the occurrence of kidney stones could be detected. Regression analysis identified hypertension and HOMA-IR values as the independent variables able to predict eGFRcr-cys in PHPT patients. Considering the occurrence of cardiovascular diseases (CVD) (coronaropathy, arithmopathy, and cerebral vasculopathy), after adjustment for age and sex, CVD was positively correlated with cystatin C levels (β 0.305 ± 0.109; $P=0.006$) and negatively with eGFRcr-cys values (β -0.005 ± 0.002; $P=0.011$). In conclusion, elevated cystatin C levels were cross-sectionally associated with key CVD risk factors and with CVD diseases in PHPT patients as in the general population.
Disclosure
This work was supported by IRCCS Policlinico San Donato Research Found.

DOI: 10.1530/endoabs.37.GP.10.09

GP.10.10

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

Claire Vahe[1], Marie-Francoise Odou[1], Rachel Desailloud[2], Clara Leroy[1], Catherine Bauters[1], Arnaud Scherpereel[1], Francois Pattou[1], Bruno Carnaille[1], Jean-Louis Wemeau[1] & Marie-Christine Vantyghem[1]
[1]CHRU Lille, Lille, Nord, France; [2]CHU Amiens, Amiens, Picardie, France.

Calcium-sensing receptor gene (CASR) loss-of-function mutations lead to familial hypocalciuric hypercalcaemia (FHH), neonatal severe hyperparathyroidism, and primary hyperparathyroidism. FFH is characterized by mild hypercalcaemia, hypocalciuria, calcium clearance/creatinine clearance (CaCl/CrCl) <0.01, normal or high PTH level. Nevertheless the phenotype may vary (Thakker 2012). The aim of this work was to compare the phenotypes of patients bearing or not a pathogenic *CASR*-mutation. Patients included ($n=131$; 96 females, median (IQR) age 63 (40–77)) referred either for a calcium disorder not explained by sporadic hyperparathyroidism ($n=118$) or pulmonary hypertension ($n=13$ controls), were sequenced for *CASR* gene after written informed consent. Patients taking diuretics, diphosphonates, lithium, with kidney failure, CaSR-antibodies or gain-of-function *CASR*-mutations had been excluded. Gender, age, nephrolithiasis, bone DEXA, blood calcium, phosphate, creatinine, 25-hydroxyvitamin D and PTH levels, 24-H calciuria, and CaCl/CrCl were compared according to the level of calcaemia <100, 100–105, or >105 mg/l and the presence of a pathogenic *CASR* mutation. The *CASR*-mutated group ($n=21$) showed higher calcaemia (108 (105–116) mg/l vs 105 (98–111) mg/l) and lower PTH (50 (32–91) pg/ml vs 83 (52–107) pg/ml) than the non-mutated group ($n=110$), with no difference for other parameters, especially 25-hydroxyvitamin D (27 (21–35) ng/ml vs 23 (15–33) ng/ml, calciuria (120 (45–183) mg/24 h vs 123 (65–188) mg/24 h), and CaCl/CrCl (0.01 (0.00–0.02) vs 0.01 (0.01–0.02)). The non-mutated group included 51 normal CASR, 50 heterozygous, and nine homozygous or composite heterozygous variants. The comparison of these three sub-groups with the *CASR*-mutated group also differed for calcaemia and PTH ($P=0.01$). *CASR*-mutations and CASR-variants were identified respectively in none and 15 (53%) of the 28 patients with calcaemia <100 mg/l, 4 (14%) and 14 (50%) of the 28 patients with calcaemia between 100 and 105 mg/l, and 17 (22%) and 30 (40%) of the 75 patients with calcaemia >105 mg/l. Seven/13 (53%) patients tested without any calcium disorder bore CASR-variants.
Conclusion
50% of patients with calcaemia <105 mg/l showed a CASR-variant, whereas 40% with calcaemia >105 mg/l showed a *CASR*-mutation, with lower PTH levels, but no difference in terms of calciuria or (CaCl/CrCl) despite similar vitamin D status. Calcemia/PTH ratio could be a better marker of pathogenic *CASR*-mutation than (CaCl/CrCl) <0.01.

DOI: 10.1530/endoabs.37.GP.10.10

GP.11.01

Abstract withdrawn.

DOI: 10.1530/endoabs.37.GP.11.01

GP.11.02

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

Cafer Kaya[1], Abbas Ali Tam[1], Ahmet Dirikoç[1], Aylin Kılıçyazgan[2], Mehmet Kılıç[3], Şeyda Türkölmez[4], Reyhan Ersoy[5] & Bekir Çakır[5]
[1]Department of Endocrinology and Metabolism, Ataturk Training and Research Hospital, Ankara, Turkey; [2]Department of Pathology, Yildirim Beyazit University, Ankara, Turkey; [3]Department of General Surgery, Yildirim Beyazit University, Ankara, Turkey; [4]Department of Nuclear Medicine, Ataturk Training and Research Hospital, Ankara, Turkey; [5]Department of Endocrinology and Metabolism, Yildirim Beyazit University, Ankara, Turkey.

Introduction
Primary hyperparathyroidism (PHP) is a highly prevalent disease, which is treated most effectively by surgery. Postoperative hypocalcaemia, a morbidity of surgical treatment of parathyroidism, can prolong the hospital stay. The aim of this study was to identify the factors predictive of hypocalcaemia and hungry bone syndrome (HBS) in patients who undergo parathyroidectomy due to PHP.
Materials and methods
Preoperatively and on days 1 and 4, and month 6 postoperatively, the patients' laboratory data including parathyroid hormone (PTH), calcium, phosphorus, 25-hydroxyvitamin D3 (25-OHD), albumin, magnesium, alkaline phosphatase (ALP), blood urea nitrogen (BUN), and TSH, free T_3 and free T_4 levels; and neck ultrasonography (US) and bone densitometry findings were recorded.
Results
Hypocalcaemia was observed in 63 (38.4%) of 164 patients on day 1 following parathyroidectomy. On the postoperative 6th month, permanent hypocalcaemia was present in 10 (6.1%) patients. HBS was observed in 22 (13.4%) of the patients who underwent parathyroidectomy due to PHP. Among the PHP-related parathyroidectomy patients, postoperative hypocalcaemia was observed more frequently among patients with parathyroid hyperplasia and those with osteoporosis. On the other hand, PTH, ALP, and BUN values were higher among patients who developed HBS. Additionally, HBS was observed more frequently among osteoporosis and parathyroid hyperplasia patients and those who had thyroidectomy simultaneously with parathyroidectomy.
Conclusion
As a result, a more thorough preoperative follow-up is recommended for patients with risk factors for hypocalcaemia and HBS development.

DOI: 10.1530/endoabs.37.GP.11.02

GP.11.03

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

Husniye Baser[1], Fatma Neslihan Cuhaci[2], Oya Topaloglu[2], Fatma Yulek[3], Nagihan Ugurlu[3], Reyhan Ersoy[2], Nurullah Cagil[3] & Bekir Cakir[2]
[1]Department of Endocrinology and Metabolism, Ataturk Education and Research Hospital, Ankara, Turkey; [2]Department of Endocrinology and Metabolism, Faculty of Medicine, Yildirim Beyazit University, Ankara, Turkey; [3]Department of Ophthalmology, Ataturk Education and Research Hospital, Ankara, Turkey.

Introduction
Ocular changes are common in various endocrine disorders. However, there are only few studies reporting ocular changes in patients with primary hyperparathyroidism (PHPT). Here, we examined central corneal thickness (CCT) and retinal thickness (RT), intraocular pressure (IOP) and their relationships with serum intact parathyroid hormone (iPTH), calcium (Ca), and phosphorus levels in PHPT patients.
Methods
Thirty-seven patients with PHPT were included and compared with age- and sex-matched 43 controls. CCT, RT, and IOP were measured.
Results
There was no statistically significant difference in mean right and left RT between two groups ($P=0.730$ and $P=0.530$ respectively). Right CCT and IOP were significantly higher than controls ($P=0.024$ and $P=0.038$ respectively). However, no significant difference was found between groups concerning left CCT and IOP ($P=0.415$ and $P=0.070$ respectively). A negative correlation was observed between right CCT, and serum phosphorus and 24-h urine phosphorus levels ($r=-0.391$, $P=0.017$ and $r=-0.393$, $P=0.021$ respectively). Additionally, right IOP was negatively correlated with 24-h urine calcium levels ($r=-0.331$, $P=0.049$). Left CCT was negatively correlated with 24-h urine phosphorus levels ($r=-0.348$, $P=0.044$). Furthermore, negative correlation was found between left IOP and 24-h urine calcium levels ($r=-0.396$, $P=0.017$). No significant correlation was found between iPTH levels and right CCT, right RT, right IOP, left CCT, left RT, and left IOP levels ($P>0.05$ for all parameters). Also, serum Ca levels were not significantly correlated with right CCT, right RT, right IOP, left CCT, left RT, and left IOP levels ($P>0.05$ for all parameters).
Conclusion
In the literature, data about ocular diseases and PHPT are rare. In this study, we observed right CCT and IOP values of patients with PHPT were significantly higher than controls. We consider that the identification of ocular aspects of PHPT is significant, and further studies related to the condition are required.

DOI: 10.1530/endoabs.37.GP.11.03

GP.11.04

Secondary hyperparathyroidism in HIV patients and its relation to cardiovascular risk factors

Manuel Cayón Blanco, Carolina García-Figueras Mateos, Rosa Marquez Pardo, Patricia Bancalero Herrera, Alberto Terrón Pernía & Salvador Pérez Cortés
Hospital SAS Jerez de la Frontera, Jerez de la Frontera, Andalusia, Spain.

Rationale
Low level of vitamin D can results in secondary hyperparathyroidism (SH) that has been linked to increased cardiovascular risk in general population. However, the spectrum of cardiovascular risk associated with SH in HIV-infected adults remains uncertain. Our main aim was to determine its potential association with different markers of cardiovascular risk in HIV-infected adults.
Methods
Cross-sectional study. Clinical data related to obesity, blood pressure, glucose metabolism, lipid profile, toxics use, and renal function were recorded. Hypovitaminosis D was defined by 25-hydroxy vitamin D level <30 ng/ml. SH was defined by parathyroid hormone >65 pg/ml in presence of hypovitaminosis D. Patients were divided into three groups according to status of vitamin D and the presence of SH: A) SH and hypovitaminosis D; B) hypovitaminosis D without SH, and C) vitamin D sufficient.
Results
104 HIV patients were included. Median vitamin D was 30.6 ± 13.6 ng/ml. Prevalence of hypovitaminosis D and SH were 53.8 and 13.5% respectively. Quantitatively, all parameters related to cardiovascular risk, except fasting glycaemia, were higher among patients of group A, but only levels of total cholesterol, LDL, and triglycerides reached significant difference ($P=0.002$; 0.004; and 0.01 respectively). Also, prevalence of obesity (BMI ≥30 kg/m^2) was higher in patients that developed SH (group A) when compared to groups B and C (28.6% vs 19% vs 2%, respectively; $P=0.004$). In multivariate analysis, SH was not associated with any cardiovascular risk factor.
Conclusions
Though, HIV-infected patients with SH due to hypovitaminosis D have worse cardiovascular risk profile, we can not conclude that SH is independently associated with major risk factors. Nevertheless, we think these patients require a tighter monitoring of lipid profile, blood pressure, and renal function. Further studies will be useful to clarify the role of SH in determining unfavourable cardiovascular outcomes in HIV population.

DOI: 10.1530/endoabs.37.GP.11.04

GP.11.05

Determination of reference values for serum total 1,25-dihydroxyvitamin D_3 using an extensively validated 2D ID-UPLC–MS/MS method

Niek Dirks[1], Frans Martens[1], Dirk Vanderschueren[3], Jaak Billen[3], Mariette Ackermans[2], Erik Endert[2], Marinus Blankenstein[1] & Annemieke Heijboer[1]
[1]VU University Medical Center, Amsterdam, The Netherlands; [2]Academic Medical Center, Amsterdam, The Netherlands; [3]KU Leuven, Leuven, Belgium.

1,25-dihydroxyvitamin D_3, the hormonally active metabolite of vitamin D_3, tightly controls calcium blood levels. An increase of 1,25-dihydroxyvitamin D_3 leads to an increase in calcium concentration with calcium originating from various resources, including bone tissue. To assess a patient's vitamin D status the precursor metabolite 25-hydroxyvitamin D_3 is determined. However, measurement of 1,25-dihydroxyvitamin D is required when disorders of 1α-hydroxylation, extrarenal 1α-hydroxylation, or vitamin D receptor defects are suspected. The aim of this study was to determine reference values for 1,25-dihydroxyvitamin D_3 using a 2D ID-UPLC–MS/MS method.
The 2D ID-UPLC–MS/MS method (Xevo TQ-S tandem quadrupole mass spectrometer and an Acquity UPLC system (Waters)), able to measure picomolar concentrations of 1,25-dihydroxyvitamin D_3 in human serum, was extensively validated with regard to sensitivity, specificity, and robustness. Intra-assay variation was $<5\%$ and inter-assay variation was $<7.5\%$ over the whole dynamic range. Limit of quantitation was 3.4 pmol/l. Our method correlated well with a published 1,25-dihydroxyvitamin D_3 LC–MS/MS method (Vanderschueren *et al*. *J Clin Endocrinol Metab* 2013) ($r=0.98$) and with the average 1,25-dihydroxyvitamin D results of the vitamin D External Quality Assessment Scheme (DEQAS) determined with LC–MS/MS ($r=0.93$).
Reference values determined in 96 plasma samples of healthy volunteers (46 women and 50 men, aged 20–70 years) were 59–159 pmol/l (non-parametric 95% CI). The female part of the reference group showed a statistically significant decrease of 1,25-dihydroxyvitamin D_3 concentration with age. The presence of significantly higher average 1,25-dihydroxyvitamin D_3 levels in premenopausal women taking oral anticonceptive pills compared to postmenopausal women suggests that this effect is estrogen-related.
In conclusion, we described a 2D ID-UPLC–MS/MS method able to measure 1,25-dihydroxyvitamin D with a high sensitivity and precision. In addition, references values for 1,25-dihydroxyvitamin D were established using this method.

DOI: 10.1530/endoabs.37.GP.11.05

GP.11.06

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

Araceli Muñoz-Garach[1], Mercedes Clemente-Postigo[2], Diego Fernandez-García[1], Fernando Cardona-Diaz[2], Manuel Macias-Gonzalez[2] & Francisco Tinahones-Madueño[1,2]
[1]University Hospital Virgen de la Victoria, Málaga, Spain; [2]Laboratorio de Investigación Biomédica, Fundación IMABIS, Málaga, Spain.

Introduction
25-hydroxyvitamin D (25(OH)D3) deficiency has been associated with diabetes and obesity. However, the mechanisms underlying these relationships are not completely understood. Vitamin D receptor (VDR) is expressed in adipose tissue; it has been reported a higher expression in obese patients than in lean subjects, suggesting a differential vitamin D dynamics in adipose tissue according to the obesity degree. In addition, 1, 25-dihydroxyvitamin D3 (1,25(OH)2D3) is able to modify VDR gene expression in mice 3T3-L1 preadipocytes.
Objective
To analyse plasma 25(OH)D3 and VDR gene expression in adipose tissue according to BMI and glycemic status. To evaluate the influence of 1,25(OH)2D3 and VDR gene expression in human adipose tissue cultures.
Materials and methods
We recruited and classified 119 subjects according to their BMI (lean, overweight, obese, and morbidly obese subjects) and to their glycemic status: normoglycemic (NG) and prediabetic/diabetic (P/D) patients. We measure plasma 25(OH)D3 and parathyroid hormone (PTH) levels as well as VDR gene expression in visceral adipose tissue. Adipose tissue from morbidly obese (ATMO) and lean (ATL) donors were cultured and treated with a range of 1,25(OH)2D3 concentrations.
Results
Plasma 25(OH)D3 were lower in P/D patients compared to NG subjects in the four BMI groups ($P<0.05$). Plasma 25(OH)D3 levels correlated negatively with HOMA-IR ($P<0.01$) and glucose ($P<0.05$). No differences were found in plasma 25(OH)D3 levels according to the BMI. There was a higher VDR gene expression levels in morbidly obese patients ($P<0.05$) compared to groups with lower BMI. 1,25(OH)2D3 increased VDR gene expression in ATMO, but not in ATL ($P<0.05$).
Conclusion
Plasma 25(OH)D3 are diminished in P/D patients compared to NG subjects independently of BMI and are closely related with glucose metabolism variables, suggesting that vitamin D deficiency is associated more with carbohydrate metabolism than with obesity. Adipose tissue VDR gene expression was significantly higher in morbidly obese patients than in the other BMI groups and its regulation by 1,25(OH)2D3 was only demostrated in morbidly obese subjects.

DOI: 10.1530/endoabs.37.GP.11.06

GP.11.07

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

Eva Feigerlova[1,3], Essi Ewu[3], Shyuefang Battaglia[2,3], Brigitte Leininger[3], Georges Weryha[2] & Jean-Louis Gueant[2,3]
[1]Centre Hospitalier Universitaire, Poitiers, France; [2]Centre Hospitalier Universitaire, Nancy, France; [3]INSERM U954, Université de Lorraine, Nancy, France.

Folate and cobalamin are methyl donors (MD) needed for synthesis of methionine, precursor of *S*-adenosylmethionine (SAM), the substrate of methylation in epigenetic, and epigenomic pathways. The MD deficiency (MDD) leads to a decrease in SAM/SAH ratio and hyperhomocysteinemia, which has been related to osteoporosis in humans and disruption of development of epiphyseal cartilage in rat. However, the underlying molecular mechanisms remain elusive.
Method
We studied the consequences of MDD on proliferation and differentiation of MG-63 pre-osteoblasts.
Results
$1,25(OH)_2D_3$ and vehicle treated MDD cells displayed a significantly decreased nuclear expression of PGC-1α/VDR complex comparing to controls. The impaired activation of PGC-1α in deficient cells resulted from its decreased methylation related to the blunted methyl-transferase activity, and increased cellular concentration of SAH, a potent inhibitor of PRMT1. Hypomethylation of PGC-1α dramatically affected expression of differentiation markers in deficient cells with a strong increase in PPARγ and its targets (adiponectin and ERRα), and a significantly decreased expression and activity of bALP. The MDD induced a marked increase in expression of the HSP90. Although primarily cytoplasmic, HSP90 has been shown to translocate to nucleus and play a role in regulation of NR activity. In this study, strong HSP90-VDR interactions in the MDD cells make VDR less likely to bind to the PGC-1α. We suppose that the HSP90-VDR impaired formation of the VDR/NR heterodimer, with an increased expression of PPARγ targets (adiponectin and ERRα) leading to an adipogenic phenotype. Treatment with SAM rescued effects of $1,25(OH)_2D_3$ on VDR/NR normalizing expression of PPARλ, ERRα, adiponectin. Addition of AdoX, an inhibitor of methyltransferase activity, produced similar changes as MDD.
In conclusion, this is the first evidence demonstrating existence of functional interactions between PGC-1α and VDR, its key role for normal functioning of the VDR-NR transcriptional co-regulation during osteoblast differentiation, and a dramatic effect of MDD on this co-regulatory network.

DOI: 10.1530/endoabs.37.GP.11.07

GP.11.08

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

Renate de Jongh[1], Renée de Mutsert[2], Paul Lips[1], Frits Rosendaal[2] & Martin den Heijer[1,2]
[1]Department of Internal Medicine, VU Medical Center, Amsterdam, The Netherlands; [2]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands.

Introduction
Obesity is associated with lower serum 25-hydroxyvitamin D (25(OH)D) concentrations. A major explanatory hypothesis is that vitamin D is sequestered

by adipose tissue. Another hypothesis is a decreased hepatic activation by 25-hydroxylase in obese individuals. Because adipose tissue has different characteristics and functions in different parts of the body an important question is whether serum 25(OH)D is more strongly related to visceral (VAT), hepatic, or total body fat (TBF).
Methods
In the Netherlands Epidemiology of Obesity (NEO) study, a cohort of 6671 men and women, VAT was assessed by MRI in combination with ^{1}H-MR spectroscopy of hepatic triglyceride content (HTGC) in 2076 participants. TBF was determined with bioelectrical impedance analysis and serum 25(OH)D was measured. We performed linear regression of VAT and HTGC on serum 25(OH)D, adjusted for age, sex, ethnicity, smoking, education, alcohol consumption, and TBF.
Results
After exclusion of alcohol abuse ($n=117$) and missing data ($n=24$), 1935 participants were analysed (mean and S.D. of age: 55 (6) years, BMI: 26 (4) kg/m^2, VAT: 87 (54) cm^2, HTGC: 5.6 (7.7), serum 25(OH)D: 62.7 (26.7) nmol/l, 56% women). Per S.D. of VAT serum 25(OH)D was 5.3 nmol/l (95% CI −7.5, −3.2) lower, and per S.D. HTGC 3.3 nmol/l (−3.6, −0.4) lower. Per S.D. of total body fat serum 25(OH)D was 5.7 nmol/l (−8.1, −3.2) lower. In a joint model including VAT, HTGC, and TBF, only VAT remained negatively associated with serum 25(OH)D (−4.9 nmol/l; −7.1, −2.7 per S.D.).
Conclusion
The major finding of the present study is that although all markers of total and regional adiposity were associated with lower serum 25(OH)D, joint models showed that visceral adipose tissue was most strongly related to lower serum 25(OH)D concentrations.

DOI: 10.1530/endoabs.37.GP.11.08

GP.11.09

Physical performance in women with vitamin D deficiency

Cristina Capatina[1,2], Mara Carsote[1,2], Mihai Berteanu[3,4] & Catalina Poiana[1,2]
[1]Department of Endocrinology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; [2]C.I. Parhon National Institute of Endocrinology, Bucharest, Romania; [3]Department of Physical Medicine and Rehabilitation, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; [4]Department of Physical Medicine and Rehabilitation, Elias Emergency Hospital, Bucharest, Romania.

Introduction
VD deficiency is associated with the atrophy of muscle fibres (predominantly type II). This leads to decreased muscle force and general physical performance.
Objective
To analyse the relationship between the serum concentration of 25-hydroxy vitamin D (25OHD), balance and physical performance in women with VD deficiency and the effect of VD supplementation or treatment with a VD analog.
Materials and methods
We analysed 105 women of various ages with VD deficiency defined as a serum concentration of 25OHD below 30 ng/ml. We recorded the results of the balance Tinetti scale, chair-rise test (CRT) and timed-up-and go test (TUG). We randomised the patients to receive colecalcipherol 1000 IU daily or alphacalcidol 1 μg daily, together with 500 mg calcium. The treatment was administered for 6 months.
Results
The subjects were aged between 20 and 83 years old (mean ± S.D. 51.95 ± 12.77 years). The mean baseline 25OHD concentration was 12.68 ± 5.77 ng/ml (mean ± S.D.). The Tinetti balance subscore was significantly correlated with the concentration of 25OHD ($P=0.022$). The mean results at the TUG and CRT test were 8.91 ± 2.46 and 15.34 ± 5.58 s respectively. After treatment, the mean results at TUG and CRT test became 8.5 ± 2.17 and 14.56 ± 5.56 s respectively ($P=0.000$ compared to baseline) representing a mean change of −4.9 and −7.33% respectively. The global Tinetti score and the subscores for balance and posture also improved significantly compared to baseline ($P=0.000$ for total score and balance subscore and $P=0.033$ for posture). The results were significantly better in the subgroup treated with alphacalcidol compared to the subgroup offered cholecalciferol for TUG ($P=0.012$) but not for CRT ($P=0.074$) . No difference was noted in the evolution of the Tinetti score between the treatment subgroups.
Conclusions
The major finding of the present study is that VD deficiency is significantly correlated with poor physical performance and impairment of balance and the effects are partially reversible with either VD supplementation or active VD analogs (alphacalcidol).

DOI: 10.1530/endoabs.37.GP.11.09

Diabetes and obesity - Translational diabetes

GP.12.01

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

Murat Karakulak[1], Muzaffer Temur[2], Özgür Yilmaz[2], Ugur Saygili[3], Elif Pelin Özün Özbay[4], Mehmet Calan[5] & Hese Cosar[6]
[1]Department of Obstetrics and Gynecology, Silivri State Hospital, Istanbul, Turkey; [2]Department of Obstetrics and Gynecology, Manisa Merkezefendi Hospital, Manisa, Turkey; [3]Department of Obstetrics and Gynecology, Dokuzeylul University Medical School, Izmir, Turkey; [4]Department of Obstetrics and Gynecology, Aydin Obstetrics and Pediatrics Hospital, Aydin, Turkey; [5]Department of Endocrinology, Bozyaka Research Hospital, Izmir, Turkey; [6]Division of Neonatology, Department of Pediatrics, Manisa Merkezefendi Hospital, Manisa, Turkey.

Purpose
The purpose of this study was to analyse ghrelin concentrations in the umbilical cord of pregnant women with a diagnosis of gestational diabetes mellitus. The relationship between ghrelin concentrations and birth weights was investigated.
Methods
Sixty pregnant women with gestational diabetes mellitus and 64 healthy pregnant women with three oral glucose tolerance test results within normal limits were included in the study. Following birth but before extraction of the placenta, 10-ml blood samples were drawn from the umbilical vein in both groups. Ghrelin concentrations were measured.
Results
The mean birth weights of the babies born to mothers with GDM were higher than those in the control group ($P=0.04$). The cord blood ghrelin levels in pregnant women with GDM were significantly lower than those of the healthy women in the control group (879.6 pg/ml vs 972.2 pg/ml; $P=0.03$). The umbilical cord blood ghrelin concentrations in pregnant women with GDM undergoing insulin therapy were significantly lower than those of the control group (792.61 pg/dl vs 972.2 pg/dl; $P=0.01$). Inverse correlations were detected between umbilical cord blood ghrelin levels and birth weights of the babies both in the group with GDM patients (r: −0.785; $P=0.001$) and in the control group (r: −0.749; $P=0.001$).
Conclusions
In pregnant women with GDM, umbilical cord ghrelin concentrations are closely related to the birth weights of the babies. Ghrelin presumably may be among the factors influencing foetal development potentially with its GH stimulating effects or by means of other mechanisms.

DOI: 10.1530/endoabs.37.GP.12.01

GP.12.02

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

Yelena Aghajanova & Maria Badalyan
Yerevan State Medical University, Yerevan, Armenia.

Introduction
Embryonal antitumour modulator of Mkrtchyan (EATM) reveals a hypoglycemic effect in streptozotocin-induced diabetes in rats. The aim of the work was to determine the influence of EATM on the process of releasing of Nox of erythrocyte membranes (EM) and serum of patients with diabetes type 1 and 2.
Materials and methods
The study included 12 patients with type 1 diabetes, 12 patients with type 2 diabetes and 12 healthy volunteers. Isolation of Nox fractions of purified EM and blood serum was performed by ion-exchange chromatography. The Nox amount was determined at 530 nm. O_2^--producing activity of Nox isoforms was determined by nitrotetrazolium blue. The statistical analysis was performed by one-way ANOVA. The study was approved by the Local Ethics Committee of the YSMU.
Results
It was shown, that the Nox release in EM of type 2 and 1 diabetes is higher by 83.3 ± 7.4% and 58.4 ± 6.5%, respectively, compared with donor blood. The addition of EATM resulted in suppression of the process of the Nox release in EM in diabetes type 2 and 1 and healthy donors by 45.5 ± 6.2%, 31.6 ± 4.4% and 25.1 ± 3.7%, respectively. In the same conditions the increase of releasing of the extracellular Nox from the blood serum in diabetes type 2 and 1 is up by 109.2 ± 8.7% and 45.4 ± 5.5% respectively. Addition of EATM reduced activity of eNox by 47.9 ± 4.4%, 31.3 ± 2.9% and 29.3 ± 3.2%, respectively.
Conclusion
The suppression of the releasing Nox and eNox of EM and serum exosomes in diabetes type 1 and 2 may be apparently a novel mechanism of membrane

stabilising effect of the EATM *ex vivo*. This gives some scientific term for EATM as an agent, which helps to stabilise the EM and exosomes in diabetes type 1 and especially type 2 *in vivo*.

DOI: 10.1530/endoabs.37.GP.12.02

GP.12.03

Can physical activity modify the impact of the genes on the incidence of type 2 diabetes mellitus?

Lukasz Szczerbinski[1], Witold Bauer[2], Joanna Goscik[3], Natalia Wawrusiewicz-Kurylonek[1], Magdalena Paczkowska[2], Magdalena Niemira[2], Anna Citko[2], Michal Ciborowski[2], Katarzyna Maliszewska[1], Edyta Adamska[2], Adam Kretowski[1,2] & Maria Gorska[1]
[1]Department of Endocrinology, Diabetology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland; [2]Clinical Research Centre, Medical University of Bialystok, Bialystok, Poland; [3]Centre for Experimental Medicine, Medical University of Bialystok, Bialystok, Poland.

The exact mechanism of the development of T2DM is still unclear, however, it is known that important role is played by both environmental and genetic factors. In this study we focused on describing the interactions between environmental and genetic factors and answering the question whether physical activity can modify the impact of the genes on the incidence of T2DM. We recruited 921 subjects (median age: 38 years; 49.7% man; mean BMI: 28.1) from the cohort 1000 Polish Longitudinal University Study (PLUS). PA has been assessed using International Physical Activity Questionnaire, and 37 single nucleotide polymorphisms (SNPs) associated with T2DM in GWAS have been genotyped, to explore interaction between the SNPs and the level of PA on the incidence of T2DM. Genetic risk score (GRS) as a weighted sum of risk alleles have been calculated. We also calculated the percentage of T2DM cases within each of the four strata given by high and low GRS and PA using R software. To explore GRS and PA interactions, we examined associations of PA with T2DM in each group. The incidence of T2DM was lower among physically active individuals in high GRS group (8.6% in high PA class vs. 13.8% in low PA class, $P < 0.03$) as well as in low GRS group (4.4% in high PA class vs 8.7% in low PA class, $P < 0.03$). We also found that individuals with TT variant in rs10885122 (ADRA2A) has slightly lower values of average PA compared to those with TG and GG genotypes ($P < 0.006$). In our study we proved that the genetic predisposition to T2DM can be reduced by increasing the PA, even among patients at high genetic risk. This allows to conclude that, through the use of physical activity we can reduce the incidence of T2DM, even in patients with a genetic predisposition.

DOI: 10.1530/endoabs.37.GP.12.03

GP.12.04

Efficacy of autologous bone marrow derived mesenchymal stem cell transplantation in T2DM: a randomised placebo-controlled study

Shobhit Bhansali, Vinod Kumar, Vivekanand Jha, Neelam Marwah, N Khandelwal, Anil Bhansali & Pinaki Dutta
PGIMER, Chandigarh, India.

Introduction
There is a growing interest in cell-based therapies in T2DM as β-cell failure is progressive and inexorable. This study evaluates the efficacy of autologous bone marrow-derived mesenchymal stem cell transplantation (ABM-MSCT) in T2DM.
Methods
This prospective, randomised, single-blinded placebo-controlled study enrolled 20 patients with triple oral hypoglycaemic drug failure and requiring insulin $\geq$0.4 Units/kg per day for achieving euglycaemia (HbA1c $\leq$7.5%). They were randomly assigned to mesenchymal stem cells (MSCs) group ($n=10$) who received ABM-MSCT through targeted approach, while control arm ($n=10$) underwent sham procedure and were followed for 6 months. The efficacy of intervention was assessed by gold standard method 'hyperglycaemic clamp' to estimate C-peptide response. The primary endpoint was a reduction in insulin requirement by 50% from baseline, while maintaining HbA1c $\leq$7%.
Results
Six out of the 10 (60%) patients in the ABM-MSCT, while 1 (10%) in the control group achieved the primary endpoint ($P=0.05$). The insulin requirement decreased by 45% in the ABM-MSCT group from 45.5 (34.0–52.2) IU/day to 25 (15.0–32.5) IU/day ($P=0.0001$), while in controls it decreased by 4% from 52.0 (40.0–82.0) IU/day to 50 (22.0–58.0) IU/day ($P=0.001$) with significant reduction between both the groups at 6 months ($P=0.047$). There was a modest but significant decrease in HbA1c in cases from 6.9% (6.6–7.0%) to 6.8% (6.1–7.2%) ($P=0.001$) as well as in controls from 6.6% (6.1–6.8%) to 6.2% (6.0–6.2%) ($P=0.001$), but it was not significant between the groups ($P=0.32$). There was a significant decrease in 2nd phase C- peptide response during hyperglycaemic clamp ($P=0.004$) and HOMA-β (0.04) without any significant change in HOMA-IR ($P=0.08$).
Conclusion
The ABM-MSCT results in decrease in insulin requirement while maintaining HbA1c $\leq$7%. However, the mechanism/s related to improvement in glycaemia remains elusive.

DOI: 10.1530/endoabs.37.GP.12.04

GP.12.05

Telomere biology and vascular ageing in patients with T2DM

Nataliia Brailova[1], Ekaterina Dudinskaya[1], Irina Strazhesko[1], Dariga Akasheva[1], Marina Pokrovskaya[1], Olga Tkacheva[1], Sergei Boytsov[1], Marina Shestakova[2] & Vladimir Vigodin[1]
[1]National Research Centre for Preventive Medicine, Moscow, Russia; [2]National Research Centre for Endocrinology, Moscow, Russia.

It is known that glucose disturbances contribute to vascular ageing. The length of telomere (TL) and telomerase activity (TA) are considered as biomarkers of cellular ageing. It is crucial to determine the role of telomere biology in different vessels changes in diabetic patients. The aim of our study was to determine the role of telomere biology in vascular ageing in patients with T2DM.
Methods
The study group included 50 patients with T2DM in mean age 58.4±7.83 years. All subjects were measured for TL and TA by quantitative polymerase chain reaction (PCR), fasting plasma glucose (FPG), glycated HbA1c; oxidative stress marked by malondialdehyde (MDA); inflammation marked by IL-6, C-reactive protein (CRP); arterial stiffness (AS) evaluated by carotid-femoral pulse wave velocity (PWV); carotid intima-media thickness (IMT), plaque presence (PP) and endothelial dysfunction evaluated by flow-mediated endothelium-dependent vasodilation (FMV) and endothelium-independent vasodilation (NDV).
Results
All patients were divided into two groups by the median of TL (9.75): «short» telomeres and «long» telomeres. Vessels changes were more pronounced in patients with «short» TL: PWV 14.11±3.22 m/s vs 11.78±3.26 m/s ($P=0.016$), IMT 1.00±0.15 mm vs 0.84±0.16 mm ($P=0.0010$), PP 2.63±0.31 vs 1.36±0.26 ($P=0.0032$), FMV 7.93±3.40 vs 10.95±3.10 ($P=0.0022$), NDV 12.63±4.25 vs 15.68±4.51 ($P=0.0186$). TA was similar in the two groups. We found increasing of oxidative stress and chronic inflammation in diabetic patients with «short» TL: MDA 3.43±1.06 mkmol/l vs 2.94±0.87 mkmol/l ($P=0.058$); CRP 9.43±2.01 mg/l vs 3.30±0.37 mg/l ($P=0.0062$). Correlation analysis showed significant association between TL and next parameters: PWV ($r=-0.50$, $P=0.0003$), IMT ($r=-0.39$, $P=0.0059$), FMV ($r=0.49$, $P=0.0003$), NDV ($r=0.41$, $P=0.0035$), FPG ($r=-0.42$, $P=0.0027$), CRP ($r=-0.40$, $P=0.0039$), TA ($r=-0.32$, $P=0.0353$).
Conclusion
In patients with T2DM and 'short' telomeres signs of vascular ageing, chronic inflammation and oxidative stress were more pronounced. Perhaps long telomeres protect vessels of patients with T2DM from accelerated vascular ageing.

DOI: 10.1530/endoabs.37.GP.12.05

GP.12.06

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

Charalampos Tsentidis[1], Dimitrios Gourgiotis[2], Lydia Kossiva[1], Antonios Marmarinos[2], Artemis Doulgeraki[3] & Kyriaki Karavanaki[1]
[1]Diabetic Clinic, Second Pediatric Department University of Athens, Athens, Attica, Greece; [2]Biochemistry Laboratory, Second Pediatric Department University of Athens, Athens, Attica, Greece; [3]Department of Bone and Mineral Metabolism, Institute of Child Health, 'Aghia Sophia' Children's Hospital, Athens, Attica, Greece.

Introduction
T1DM is a risk factor for reduced bone mass, disrupting several bone metabolic pathways. Dickkopf-1 is an inhibitor of the Wnt/b-catenin bone metabolic pathway. Increased fracture risk and elevated Dickkopf-1 levels have been documented in adult patients with T2DM. No relevant data exist on childhood T1DM. Our aim was to study plasma Dickkopf-1 concentration in children and adolescents with T1DM and controls and to correlate Dickkopf-1 levels with metabolic bone markers and bone mineral density (BMD).
Methods
Forty children and adolescents with T1DM were evaluated (mean ± S.D. age: 13.04 ± 3.53 years, T1DM duration: 5.15 ± 3.33 years), along with 40 healthy matched controls (mean ± S.D. age 12.99 ± 3.3 years). Dickkopf-1, Sclerostin, osteocalcin, C-telopeptide crosslinks-CTX, electrolytes, PTH, total 25(OH) D were measured, while lumbar spine and total body BMD were evaluated.
Results
BMD was significantly lower in T1DM patients than controls. Dickkopf-1 levels demonstrated a Gaussian distribution, with higher levels in T1DM patients (13.56 ± 5.34 vs 11.35 ± 3.76 pmol/l, $P = 0.0194$). A trend for lower values was found in girls (13.36 ± 4.04 vs 11.72 ± 5.14 pmol/l, $P = 0.06$) and in pubertal children (13.61 ± 4.87 vs 11.83 ± 4.56 pmol/l, $P = 0.054$). Dickkopf-1 correlated with Sclerostin and L1-L4 BMD z-score only in controls and with Osteoprotegerin and i-Phosphorus only in patients, while in both groups a significant correlation with log(CTX) and √ALP was documented. A significant correlation of Dickkopf-1 with IGF-1 and insulin dose was also shown in patients.
Conclusion
T1DM children and adolescents had higher levels of Dickkopf-1 than controls, indicating a downregulated Wnt signalling system and possible lower osteoblast activation that could be associated with T1DM osteopathy.

DOI: 10.1530/endoabs.37.GP.12.06

GP.12.07

GLP-1 (Active 7-36) secretory response after test meal in obese patients before and 5; 90 and 180 days after bariatric gastric bypass surgery

Dragan Micic[1], Snezana Polovina[1], Mirjana Sumarac-Dumanovic[1], Pavle Gregoric[2], Goran Cvijovic[1], Svetlana Ignjatovic[1], Marjana Dajak[1], Dusan Micic[2], Danica Stamenkovic-Pejkovic[1] & Danka Jeremic[1]
[1]Clinic for Endocrinology, Diabetes and Diseases of Metabolism, Clinical Center of Serbia, Belgrade, Serbia; [2]Emergency Center, Clinical Center of Serbia, Belgrade, Serbia.

There are different explanations concerning observed improvement of glucose control after baiatric gatric bypass surgery. The aim of our study was to investigate GLP-1 response after test meal (Fresubin drink a 200 ml; 200 kcal, 15% protein, 30% fat and 55% carbohydrate) before (day 0) and 5; 90 and 180 days after gastric bypass surgery. Glycaemia (mmol/l; glucose oxidase) and GLP-1 (Active 7-36) (pM/l; ELISA, ALPCO diagnostics) were determined in 41 obese patients (age: 37.86 ± 11.21 years; BMI: 43.45 ± 4.91 kg/m^2) in four separate days in 0, 15, 30, 45, 60, 90 and 120 min. There were significant decrease in the area under the glucose curve (X ± S.D.) (664.70 ± 186.81 vs 636.45 ± 177.35 vs 501.50 ± 90.17 vs 507.41 ± 80.08 mmol/l per min; $P < 0.05$) in respective day intervals, while there was significant increase in area under the GLP-1 curve (pmol/l per min) in days 5 (919.19 ± 653.73), day 90 (682.92 ± 489.79) and day 180 (789.41 ± 558.56) in comparison with day 0 (279.80 ± 429.97) ($P < 0.05$). There were no significant differences between basal glucose and GLP-1 levels (1.67 ± 2.64; 1.33 ± 2.12; 2.06 ± 2.75; $P > 0.05$) except for day 180 (3.52 ± 3.92 $P < 0.05$) while there was significant increase in peak GLP-1 levels in day 5 (17.12 ± 8.99), day 90 (14.44 ± 8.75) and day 180 (17.25 ± 10.52) during response after test meal in comparison with day 0 (3.82 ± 3.95) ($P < 0.05$). In conclusion, GLP-1 response after test meal is significantly increased after gastric bypass surgery early (after 5 days) and lately (after 90 and 180 days). The improvement in GLP-1 response after test meal after gastric bypass surgery may be contribute to the beneficial metabolic effects of bariatric surgery, especially concerning glucose control.

DOI: 10.1530/endoabs.37.GP.12.07

Diabetes and obesity – Translational cardiovascular and obesity

GP.13.01

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

Helen J Dranse, Jillian L Rourke, Andrew W Stadnyk & Christopher J Sinal
Dalhousie University, Halifax, Nova Scotia, Canada.

Background
Chemerin is a recently identified adipocyte-secreted signalling molecule (adipokine) that regulates adipocyte differentiation, metabolism, and inflammation through activation of the cognate receptor Chemokine-Like Receptor 1 (CMKLR1). Circulating chemerin levels are increased in obese patients as well as in patients with inflammatory bowel disease (IBD) such as Crohn's disease and ulcerative colitis. Increased white adipose tissue mass (WAT) and resultant changes in the secretion of several adipokines have been shown to negatively impact the severity and treatment of IBD. Therefore, we hypothesized that chemerin/CMKLR1 signalling represents a novel link between obesity and IBD.
Objectives
To determine whether modulation of chemerin/CMKLR1 signalling impacts weight loss, clinical illness, and colonic inflammation associated with the onset of dextran sodium sulfate (DSS)-induced colitis in mice.
Results
Chemerin and CMKLR1 expression increased in the cecum and distal colon, while CMKLR1 expression decreased in WAT, of DSS-treated mice. Following DSS treatment, WT mice had significantly higher chemerin levels both in the colon and circulation. Moreover, injection of bioactive chemerin into WT mice resulted in greater weight loss and colon inflammation compared to vehicle control. Consistent with this, CMKLR1 knockout mice exhibited decreased early weight loss and a slower onset of clinical illness compared to WT controls. However, CMKLR1-null mice exhibited similar levels of colonic inflammation and clinical illness compared to WT littermates at the final endpoint.
Conclusions
Increased levels of circulating chemerin exacerbated the severity of DSS-induced colitis and CMKLR1-null mice had a delayed onset of colitis. This suggests that chemerin/CMKLR1 signalling modulates the development of IBD.
Disclosure
This work was supported by the Canadian Institutes of Health Research (CIHR).

DOI: 10.1530/endoabs.37.GP.13.01

GP.13.02

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

Evi Aerts, Doreen Zegers[1], Laure Sorber[1], Sigri Beckers[1], An Verrijken[2], Guy Massa[3], Kim Van Hoorenbeeck[4], Stijn L Verhulst[4], Luc F Van Gaal[2] & Wim Van Hul[1]
[1]Department of Medical Genetics, University of Antwerp, Antwerp, Belgium; [2]Department of Endocrinology, Diabetology and Metabolic Diseases, Antwerp University Hospital, Antwerp, Belgium; [3]Department of Pediatrics, Jessa Hospital, Hasselt, Belgium; [4]Department of Pediatrics, Antwerp University Hospital, Antwerp, Belgium.

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

control in the hypothalamus. Genetic evidence coming from animal and association studies, has identified NPY2R as a candidate gene for obesity. Therefore we have designed an extensive mutation and CNV-analysis investigating the prevalence of genetic and structural variation in NPY2R.
Design and methods
In the first part of this study we screened 306 obese children and adolescents and 300 healthy lean individuals for mutations in the *NPY2R* coding region with high-resolution melting curve analysis. Direct sequencing was performed for samples with melting patterns deviating from WT. In the second part of this study, Multiplex Amplicon Quantification (MAQ) analysis was performed in 308 obese children and adolescents to detect copy number variation (CNV) in *NPY2R*.
Results
Mutation analysis resulted in the identification of one rare non-synonymous heterozygous variant F87I in an obese patient. Furthermore, we identified five different synonymous variants of which three (L53L, G326G and G370G) could solely be detected among obese children and two (P105P and A278A) were only present in lean individuals. L53L was identified among three different obese patients and was not present in the control population. MAQ analysis could not identify copy number variation in the *NPY2R* region in our population.
Conclusion
By performing *in silico* analysis, we determined that the F87I variant is probably damaging to the protein structure and might have a disease causing effect. Further functional testing will be necessary to fully understand the impact on NPY2R. As we could not identify any CNV in the *NPY2R* region, structural variation in NPY2R is not likely to cause obesity.
Disclosure
This work was supported by the Institute for the Promotion of Innovation through Science and Technology in Flanders (PhD grant Grant for Strategic Basic Research with grant number 121250).
DOI: 10.1530/endoabs.37.GP.13.02

GP.13.03

Effects of dietary glycaemic properties on markers of inflammation, insulin resistance and body composition in postmenopausal women
Violeta Stojkovic[1,2], Christine Simpson[1], Rebecca Sullivan[1], Anna Maria Cusano[1], Karl Insogna[1] & Jessica Bihuniak[1,3]
[1]Yale University School of Medicine, New Haven, Connecticut, USA; [2]Université de Liège, Liège, Belgium; [3]University of Connecticut, Storrs, Connecticut, USA.

Whether high glycaemic index/glycaemic load (GI/GL) diets increase low-grade inflammation leading to changes in body composition and risk for chronic illness remains uncertain. We recently completed a randomised, double-blind study comparing the effects of a 45 g whey protein supplement (PRO) and an isocaloric maltodextrin supplement (CHO) on bone density and body composition in older adults. The study afforded an opportunity to evaluate the impact of a calibrated increase in GI/GL on markers of inflammation, insulin resistance and body composition. Eighty-four postmenopausal women who consumed a minimum of 20 g of either supplement (PRO, $n=38$; CHO, $n=46$) daily for 18 months were studied. GI/GL was estimated from 3-day food records at baseline and 18 months. At the end of 18 months the GL in the CHO group increased by 34%, 88.4 ± 5.2 to 118.5 ± 4.9 ($P<0.0001$ at 18 months) and did not change in the PRO group 86.49 ± 4.14 to 81.9 ± 3.6. Despite this, there were no differences in serum CRP, IL-6, or HOMA at 18 months between the two groups, nor when the individuals in the highest quartile ($n=21$) of GL at 18 months were compared to the lowest quartile ($n=20$). However, analysis of body composition showed a significant increase in truncal lean mass ($P=0.007$) and total lean mass ($P=0.038$) in the PRO group, compared to the CHO group. In contrast, the highest GL quartile had significantly higher BMI ($P=0.03$) and total fat mass ($P=0.005$) with a significant decline in the lean/fat ratio ($P=0.0008$). Our data suggest that as dietary GL increases within the moderate range, there is no detectable change in markers of inflammation or insulin resistance, despite which there is a negative effect on lean body mass.
DOI: 10.1530/endoabs.37.GP.13.03

GP.13.04

Metabolic and gonadotropic impact of sequential obesogenic insults in the female: influence of the loss of ovarian secretion
Miguel A Sanchez-Garrido[1,3], Francisco Ruiz-Pino[1,2], Maria Manfredi-Lozano[1,2], Silvia Leon[1,2], Violeta Heras[1,2], Juan M Castellano[1,2], Maria Jesus Vazquez[1,3], Juan Roa[1,2], Antonio Romero-Ruiz[1,2], Carlos Dieguez[3,4], Leonor Pinilla[1,2] & Manuel Tena-Sempere[1,2]
[1]University of Cordoba, Cordoba, Spain; [2]Instituto Maimonides de Investigacion Biomedica de Cordoba (IMIBIC), Cordoba, Spain; [3]CIBERobn, Cordoba, Spain; [4]University of Santiago de Compostela, Santiago de Compostela, Spain.

While female fertility is known to be sensitive to conditions of low body fuel reserves, the reproductive consequences of persistent energy excess remain ill defined. Yet, the pandemic proportions of obesity, and its potential impact on the gonadotropic axis, call for a better understanding of this phenomenon. Alike, the influence of ovarian hormones on the pathophysiology of obesity and its complications merits further investigation. In this work, we aimed to elucidate the metabolic and reproductive/gonadotropic impact of various obesogenic insults in the female rat, with special attention to the influence of the loss of ovarian secretion, as model of menopause. To this end, we implemented a series of neuroendocrine studies on the metabolic and gonadotropic consequences of sequential obesogenic insults, namely, postnatal over-nutrition (SL) and high fat diet (HFD) after weaning, in gonadal-intact and ovariectomized (OVX) female rats. In young (4-mo) cyclic females, SL or HFD caused similar increases in body weight; yet, only HFD evoked additional metabolic perturbations, some of which were worsened by precedent SL. In addition, HFD caused a concomitant decrease in LH and estradiol levels, and suppressed *Kiss1* expression in the arcuate nucleus (ARC) of the hypothalamus in 4-mo females, while persistent HFD up to 10-mo induced also suppression of LH responses to kisspeptin-10. OVX caused a severe and rapid deterioration of the metabolic profile, with overweight, increased energy intake and deregulation of leptin and glucose/insulin levels; effects whose magnitude was similar, if not higher than HFD. Summation of previous obesogenic insults maximally increased body weight, basal leptin, insulin and glucose levels, and glucose intolerance. Yet, OVX obliterated the inhibitory effects of overweight/HFD on gonadotropin levels and ARC *Kiss1* expression, which were heightened due to the loss of negative feedback. In sum, our study characterizes the metabolic and gonadotropic effects of sequential exposures to obesogenic insults, and their interactions with ovarian secretions. Our data document the deleterious consequences of overweight on the female gonadotropic axis, via impairment of Kiss1 system, and substantiate the dramatic impact of OVX, as menopausal model, on the metabolic profile, especially when combined with preceding obesogenic insults.
Disclosure
This work was supported by grant BFU2011-025021 (Ministerio de Economía y Competitividad, Spain; co-funded with EU funds from FEDER Program); Projects P08-CVI-03788 and P12-FQM-01943 (Junta de Andalucía, Spain); EU research contract DEER FP7-E.
DOI: 10.1530/endoabs.37.GP.13.04

GP.13.05

The effects of cross-sex hormone therapy on body weight and fat percentage in transgender individuals
Maartje Klaver, Mariska Vlot, Marieke Dekker, Jos Megens & Martin den Heijer
VU Medical Center, Amsterdam, The Netherlands.

Introduction
Cross-sex hormone therapy is part of the treatment of individuals with gender dysphoria and affects several factors such as body composition and thereby cardiovascular risk. However, little is known about the specific effects on body weight and fat percentage in the first year of treatment.
Aim
The aim of this study is to examine the effects of cross-sex hormones on body weight and total fat percentage during the first year of treatment.
Methods
This prospective study (part of the ENIGI project) included 140 patients that completed one year of treatment. 70 male-to-female individuals (MtFs) received

cyproteronacetate (50 mg/day). Of them, 31 MtFs were treated with an estradiol patch (200 μg/week) and 39 MtFs received estradiol valerate (2–4 mg/day). 70 female-to-male individuals (FtMs) were treated, of which 39 FtMs got testosterone esters intramuscular (250 mg/2 weeks) and 4 FtMs received testosterone undecanoate intramuscular (1000 mg/12 weeks). 27 FtMs were treated with testosterone gel (50 mg/day). At the start and after 12 months of treatment their body weight was measured and a DEXA was obtained.
Results
At baseline the mean body weight of the MtFs was 77.5 kg (s.d. ± 16.8), which in one year increased to 79.7 kg (s.d. ± 17.0) with a mean difference of 2.2 kg (95% CI 0.7–3.8). Their mean total fat percentage increased with 4.0% (95% CI 3.0–5.0), from 25.0 to 29.0%. The mean body weight of the FtMs increased from 69.1 kg (s.d. ± 15.0) to 72.2 kg (s.d. ± 14.7) with a mean difference of 3.1 kg (95%CI 2.0-4.3). In FtMs, a 4.3% (95%CI −5.3 to −3.3) decrease in total fat percentage was seen, from 34.7 to 30.4%.
Conclusions
Despite an expected increase in fat percentage in MtFs and a decrease in FtMs, total body weight increased in both groups. Further research is needed to elucidate the mechanism of weight gain during cross-sex hormone treatment.

DOI: 10.1530/endoabs.37.GP.13.05

GP.13.06

Effects of testosterone replacement therapy on lean body mass, total fat mass, and insulin sensitivity in aging men with type 2 diabetes - a randomised, double-blinded, placebo-controlled trial

Line Velling Magnussen[1], Dorte Glintborg[1], Pernille Hermann[1], David M Hougaard[2], Kurt Højlund[1] & Marianne S Andersen[1]
[1]Department of Endocrinology and Metabolism, Odense University Hospital, Odense, Denmark; [2]Department of Clinical Biochemistry and Immunology, Statens Serum Institute, Copenhagen, Denmark.

Lowered testosterone levels may be observed in up to 50% of ageing men with type 2 diabetes (T2D). Testosterone replacement therapy (TRT) increases lean body mass in men with lowered testosterone levels and T2D, but the effect of TRT on glucose metabolism has not been evaluated by euglycemic hyperinsulinemic clamp.
We used gold standard methods to evaluate the effect of TRT on body composition, insulin sensitivity, and oxidative metabolism in men with T2D and lowered bio-available testosterone. Our main objective was to determine whether TRT could be a novel treatment for T2D in ageing men with lowered bio-available testosterone.
Research design and methods
A randomised, double-blinded, placebo-controlled study in 39 men, aged 50–70 years with bio-available testosterone levels <7.3 nmol/l and T2D treated with Metformin. Patients were randomized to testosterone gel ($n=20$) or placebo ($n=19$) for 24 weeks. Body composition was assessed by whole body Dual-energy X-ray Absorptiometry scans including our primary outcome, lean body mass. Whole-body insulin sensitivity was assessed by rate of insulin-stimulated glucose disposal during euglycemic hyperinsulinemic clamp. Substrate oxidation was evaluated by indirect calorimetry during euglycaemic hyperinsulinaemic clamp. Coefficients (b) represent the placebo-controlled mean effect of intervention.
Results
Lean body mass ($b=1.9$ kg, $P=0.001$) increased during TRT, while total fat mass ($b=-1.3$ kg, $b=0.009$) and HDL cholesterol ($b=-0.11$ mmol/l, $P=0.009$) decreased. Insulin-stimulated glucose disposal rate was unchanged during TRT compared to placebo ($P=0.28$). Lipid and glucose oxidation during fasting and insulin stimulation were unchanged.
Conclusions
Insulin sensitivity was unchanged in men with T2D despite significant beneficial changes in lean body mass and total fat mass after 24 weeks TRT. Furthermore, HDL cholesterol levels were reduced during TRT. Our data do not suggest testosterone replacement therapy as a novel therapy for type 2 diabetes in ageing men.
Disclosure
This study was financially supported by the Novo Nordic Foundation, Odense University Hospital, Institute of Clinical Research at the University of Southern Denmark, the Region of Southern Denmark, Consultant Council Scholarship Committee of O.

DOI: 10.1530/endoabs.37.GP.13.06

GP.13.07

Three out of four adult male patients with type 2 diabetes mellitus and symptomatic moderate to severe erectile dysfunction have hypogonadism

Jubbin Jacob[1], Raman Kumar[2] & Nitin Malhotra[2]
[1]Endocrine and Diabetes Unit, Department of Medicine, Christian Medical College and Hospital, Ludhiana, Punjab, India; [2]Department of Medicine, Christian Medical College and Hospital, Ludhiana, Punjab, India.

Context
Studies suggest that 25–40% of men with type 2 diabetes mellitus (T2DM) have hypogonadism. Other studies have estimated that 40–50% of men with T2DM have erectile dysfunction (ED). Some guidelines suggest routine measurements of testosterone in all patients with T2DM.
Objectives
To estimate the prevalence of hypogonadism in adult male patients with type 2 diabetes mellitus and symptomatic erectile dysfunction.
Methods
Consecutive adult male patients (between 30 and 60 years) with ED and T2DM attending diabetic clinic in a tertiary hospital were recruited after informed consent. Patients with psychiatric illness, renal disease, liver disease, previous pelvic surgery and major neurological diseases were excluded. ED was graded using the International Index of Erectile Dysfunction (IIEF) questionnaire. Biochemical assessment of hypothalamic-pituitary-gonadal (HPG) axis was undertaken by collecting morning samples for serum luteinizing hormone, follicle stimulating hormone, prolactin and total testosterone. These were analyzed by electrochemiluminessense assays on an ELECSYS automated system. Patients were classified as either being eugonadal or having either hypogonadotropic hypogonadism (HH) or hypergonadotropic hypogonadism (HHG).
Results
patients consented for the study with a mean age of 50.3 years and mean duration of diabetes of 5.9 years. Of them 102 patients completed all the study related procedures and were included in the analysis. 54 (52.9%) of men with T2DM and ED were eugonadal, 38 (37.3%) had HH and 10 (9.8%) had HHG. All 25 patients with mild ED (IIEF scores 17–21) were eugonadal. While of 28 patients with mild to moderate ED (IIEF scores 12–16), 24 (85.7%) were eugonadal and 4 (14.3%) had HH. Of the 16 patients with moderate ED (IIEF scores 8–11) 4 (25%) were eugonadal, 9 (56.3%) had HH and 3 (18.8%) had HHG. Among the 33 patients with severe ED (IIEF score 1–7) only 1 (3%) was eugonadal, 25 (75.8%) had HH and 7 (21.2%) had HHG ($P<0.0001$).
Conclusions
Routine hormonal evaluations of the HPG axis is probably only required in patients with moderate to severe ED with type 2 diabetes. Over 75% of patients with moderate to severe ED have subnormal total testosterone levels.

DOI: 10.1530/endoabs.37.GP.13.07

GP.13.08

Eating disorders are frequent among type 2 diabetic patients and are associated with worse metabolic and psychological outcomes: results from a cross sectional study in primary and secondary care settings

Aleksandra Speranskaya, Joana Nicolau, Luisa Ayala, Ivana Zubillaga, Pilar Sanchis, Concepcion Conchillo, Regina Fortuny & Lluis Masmiquel
Hospital Son Llatzer, Palma De Mallorca, Balearic Islands, Spain.

Objectives
Diabetes and obesity – Translational cardiovascular and obesityData regarding the prevalence of eating disorders (ED) and their influence on clinical outcomes among patients with type 2 diabetes (T2DM) are scarce. Our aim is to investigate the frequency of positive screening for ED and, specifically binge eating disorder (BED), in a T2DM sample. To analyse whether there are any differences among T2DM subjects with a positive screening for ED or BED.
Research design and methods
320 subjects with T2DM were recruited randomly. All participants were evaluated for the presence of ED by completing the 'Eating Attitudes Test-26' (EAT26). In addition the 'Questionnaire of Eating and Weight Patterns Revised' (QEWP-R) for the screening of BED was also implemented. Sociodemographic, clinical and biochemical parameters were also recorded.
Results
According to EAT26, 14% of subjects screened positive for ED. Regarding QEWP-R, 16% had a positive screening for ED, with BED having a frequency of 12.2%, being the most prevalent one. There was a positive correlation between the scores obtained with the EAT26 and the Beck Depression Inventory ($P=0.0014$). Patients with BED were younger (57.5 ± 11.1 vs 63.3 ± 10.3 years; $P=0.004$), with a lesser T2DM duration (8.5 ± 6.1 vs 12.1 ± 9.6 years; $P=0.002$).

Weight and BMI among subjects with BED were greater (89.1 ± 1.3 vs 82.4 ± 16.7 kg; $P=0.04$ and 39.4 ± 10.3 vs 30.7 ± 5.5 kg/m^2; $P=0.01$). The frequency of subjects with one admission related to T2DM or any other condition during the last year was higher (10% vs 3%; $P=0.04$ years 33% vs 21%; $P=0.01$).
Conclusions
ED among T2DM are frequent. Due to its deleterious effect on different metabolic and psychological outcomes, they should be diagnosed promptly, especially BED.
DOI: 10.1530/endoabs.37.GP.13.08

Diabetes and obesity – Clinical diabetes

GP.14.01

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

Sandra N Slagter, Robert P van Waateringe, Marjolein Wendker, Jana V van Vliet-Ostaptchouk, Helen L Lutgers, André P van Beek, Melanie M van der Klauw & Bruce H R Wolffenbuttel
Univ Med Center Groningen, University of Groningen, Groningen, The Netherlands.

Background
The metabolic syndrome (MetS) is a combination of unfavourable health factors including visceral obesity, dyslipidaemia, hypertension and impaired fasting glucose. It is also strongly associated with increased risk of cardiovascular disease (CVD) and type 2 diabetes. We assessed which factors contribute to the prevalence of MetS in people within different weight and age categories.
Methods
64 046 western European participants aged 18–80 years from the Dutch LifeLines Cohort study were categorised into three BMI classes (BMI <25, normal weight; BMI 25–30, overweight; BMI ≥ 30 kg/m^2, obese), and six age decades. MetS was defined according to the revised NCEP ATP III criteria. Within each BMI and age class, we determined the prevalence of all five MetS components.
Results
Prevalence of elevated blood pressure increased from 22% in the youngest age group (18–30 years) to 84% in the oldest age group (70–80 years). In these cohorts, the prevalence of excess waist circumference increased from 40 to 80%. The prevalence of increased serum triglycerides and fasting blood glucose was also the highest in the oldest age group (both 30%), while HDL-cholesterol remained strikingly constant with increasing age. In normal weight and overweight individuals, elevated blood pressure was the most common contributor to the presence of MetS. In obese individuals, elevated waist circumference, blood pressure and reduced HDL-cholesterol were the largest contributors.
Conclusions
The increase in prevalence of MetS with age in western European individuals is mainly driven by elevated blood pressure, and -to a lesser extent- by waist and HDL-cholesterol. As it is known that blood pressure increases with age, using a fixed 130/85 mmHg cut-off results in a disproportionate contribution of elevated blood pressure to the prevalence of MetS.
Disclosure
This work was supported by NCHA, Netherlands Consortium for Healthy Ageing, Bio-SHaRE-EU, Biobank Standardisation and Harmonisation for research excellence in the European Union. Bioresource research impact factor BRIF4568.
DOI: 10.1530/endoabs.37.GP.14.01

GP.14.02

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

Parisa Amiri[1,2], Sara Jalali-Farahani[1,2], Sakine Hanifi[1,2], Leila Cheraghi[1,2], Amir Abbas Momenan[3], Firoozeh Hosseini-Esfahani[4], Parvin Mirmiran[4], Arash Ghanbarian[3] & Fereidoun Azizi[5]
[1]Research Center for Social Determinants of Endocrine Health, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [2]Obesity Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [3]Prevention of Metabolic Disorders Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [4]Nutrition and Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [5]Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Introduction
To assess the effect of community-based multidisciplinary lifestyle interventions on metabolic syndrome (MetS) and its components in an urban population of Iranian adolescents.
Methods
This longitudinal study was conducted on 1230 adolescents, aged 12–15 years, within the framework of the TLGS. They were categorised in three groups: those residing in the intervention area during study (complete intervention group; $n=195$); those residing in the intervention area at baseline and at least one follow-up (incomplete intervention group; $n=459$) and control group ($n=576$). After baseline assessments (1999–2001), all measurements were repeated every 3 years for up to 9 years. Lifestyle interventions were aimed at achieving healthy dietary patterns and increasing the level of physical activity. The MetS has been defined using Cook definition. Generalised estimating Default (GEE) models were used to analyse data.
Results
Around 6.4, 25.3 and 10.8% of participants were lost to follow-up in control, incomplete and complete intervention groups respectively. Using GEE, at the end of study in boys, overall means of FPG were significantly lower in those who were placed in both intervention groups, compared with controls ($\beta=-3.36$ and -2.28 respectively). However, in girls only the complete intervention group had significantly lower FPG mean, vs controls ($\beta=-2.32$). In both boys and girls, mean TG was significantly lower in the complete intervention group vs controls ($\beta=-14.33$ and $\beta=-8.50$ respectively). Compared with the control group, mean SBP was significantly lower in girls of the complete intervention group ($\beta=-2.56$). Compared to controls, HDL was significantly higher in girls who received incomplete $\beta=2.17$). Among girls, the complete intervention group was less likely to have MetS and central obesity than the control group (OR = 0.23 and OR = 0.32 respectively; $P<0.05$).
Conclusion
Community-based lifestyle interventions reduced the risk of MetS and central obesity in girls and improved the means of cardio-metabolic risk factors in both sexes over the study period.
Disclosure
This research has been granted by Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences.
DOI: 10.1530/endoabs.37.GP.14.02

GP.14.03

Clinical and biological determinants of metabolically healthy obese status

Anca Sirbu[1,2], Sorina Martin[1], Carmen Barbu[1], Suzana Florea[1], Catalin Copaescu[3] & Simona Fica[1]
[1]Carol Davila University of Medicine and Pharmacy, Endocrinology Department – Elias Hospital, Bucharest, Romania; [2]Victor Babes Institute, Bucharest, Romania; [3]Ponderas Hospital, Bucharest, Romania.

Introduction
While the unfavourable metabolic consequences of obesity have been clearly demonstrated at a population level, there is a wealth of evidence indicating the existence of individuals somehow protected from developing complications, named 'metabolically healthy obese'. The aim of our study was to identify clinical and biological parameters independently associated with 'metabolically healthy' status.
Patients and methods
440 (303 women) extremely obese patients (mean BMI = 45.33 ± 8.82 kg/m^2) were clinically (medical history, anthropometrics, blood pressure (BP)) and biologically (complete metabolic tests, adiponectin, CRP, TNF-α levels) in a research programme for bariatric surgery. Metabolically healthy obese status was alternatively defined using two criteria: i) absence of metabolic syndrome (ATPIII definition) and ii) insulin sensitivity (IS) – non-diabetic patients with HOMA <2.85 were considered IS+.
Results
Only 15.8% of patients (20.4% of women) fulfilled both criteria of metabolic health. Women were IS+ in a higher percentage than men (30.7% compared with 12.4%, $P<0.001$). IS+ patients showed a lower general (BMI) and visceral (WC, WC/HC) adiposity and more favourable parameters of lipid (HDL, triglycerides) and glucose metabolism. They also had lower BP, lower chronic inflammatory markers (TNF-α, CRP), but higher levels of adiponectin. Patients without metabolic syndrome were also younger, mostly women, had a higher insulin sensitivity, lower CRP level and increased concentration of adiponectin. In logistic regression analysis, adiponectin ($P=0.011$), VAI ($P=0.012$) and uric acid ($P=0.031$) remained significantly associated with insulin sensitivity. Area under ROC curve for the model was 0.815 (IC: 0.756–0.875; $P<0.001$).

In a similar model, independent determinant of metabolic syndrome were: adiponectin ($P=0.004$), HOMA–IR ($P=0.01$) and age ($P<0.001$). Area under ROC curve for the model was 0.799 (0.744–0.853).
Conclusion
Adiponectin is an independent determinant of metabolically healthy obese status, disregarding the criteria used for its definition.
Disclosure
This work was partly supported by the Sectorial Operational Programme Human Resources Development (SOPHRD), financed by the European Social Fund and the Romanian Government under the contract number POSDRU 141531.
DOI: 10.1530/endoabs.37.GP.14.03

GP.14.04

Parental obesity in association with offspring cognitive and psychomotor development at 4 years of age: the mother child 'Rhea' cohort in Crete, Greece

Vasiliki Daraki[1,2], Vaggelis Georgiou[1], Katerina Koutra[1], Andriani Kyriklaki[1], Mariza Kampouri[1], Katerina Sarri[1], Maria Vassilaki[1], Stathis Papavasiliou[2], Manolis Kogevinas[1] & Leda Chatzi[1]
[1]Department of Social Medicine, Faculty of Medicine, University of Crete, Heraklion, Greece; [2]Department of Endocrinology Diabetes and Metabolic Diseases, University Hospital of Crete, Heraklion, Greece.

Introduction
Animal studies suggest that maternal obesity may impact foetal brain structure and function and increase long-term susceptibility to neurodevelopmental and neuropsychiatric disorders. Few human studies have examined these associations with conflicting results. It is unclear if reported associations are due to genetic background or intrauterine mechanisms.
Objective
To investigate the association of maternal and paternal obesity status with offspring cognitive and psychomotor development at 4 years of age using data from a longitudinal, prospective pregnancy cohort, 'Rhea' study in Crete, Greece.
Design and methods
The present study includes 652 mother-child pairs, after excluding twin pregnancies and women with pre-gestational diabetes. Pre-pregnancy maternal BMI and paternal BMI were calculated at the first prenatal visit (mean: 12 weeks, S.D.: 1.5) neurodevelopment at 4 years was assessed by means of the McCarthy Scales of Children's Abilities (MSCA). Emotional and behavioural development at 4 years was assessed by means of Strengths and Difficulties Questionnaire (SDQ) and Attention Deficit Hyperactivity Disorder (ADHD) Test. Multivariable linear regression models were used to estimate the effect of pre-pregnancy BMI and paternal BMI on child neurodevelopment at 4 years of age after adjusting for multiple confounders.
Results
Maternal obesity pre-pregnancy was associated with reduced general cognitive (score reduction: −2.51; 95% CI: −4.78, −0.24), quantitative (score reduction: −2.50 95% CI: −4.89, −0.11) and memory development scores (score reduction: −2.66 95% CI: −5.07, 0.26) at 4 years of age. These associations were more pronounced in girls compared to boys. No association was found between pre-pregnancy BMI and child emotional and behavioural development or ADHD symptoms at 4 years of age. Paternal BMI was not associated with offspring cognitive and behavioural development at 4 years of age.
Conclusion
Maternal pre-pregnancy BMI was associated with reduced cognitive development at preschool age. This association appeared more likely to be due to intrauterine mechanisms than shared family and social characteristics.
Disclosure
This work was supported by the 'Program of prevention and early diagnosis of obesity and neurodevelopment disorders in preschool age children in the prefecture of Heraklion, Crete, Greece' (NSRF 2007-2013 project, MIS 349580), co-f.
DOI: 10.1530/endoabs.37.GP.14.04

GP.14.05

The effect of Roux-en-Y gastric bypass, sleeve gastrectomy and adjustable gastric banding on renal function and remission of metabolic disease: a five-year longitudinal study

Karl Neff[1], Gregory Baud[2], Violeta Raverdy[2], Carel le Roux[1] & Francois Pattou[2]
[1]Diabetic Complication Research Centre, UCD Conway Institute, School of Medicine and Medical Science, University College Dublin, Dublin, Ireland; [2]Department of General and Endocrine Surgery, Lille University Hospital, Lille, France.

Introduction
There are few data on renal function following bariatric surgery. We evaluated the effect of Roux-en-Y gastric bypass (RYGB), adjustable gastric banding (AGB) and sleeve gastrectomy (SG) on renal function over a 5-year post-operative period. We also evaluate the effect of these procedures on remission of diabetes and hypertension.
Methods
Analysis of a prospectively collected database at Lille University Hospital. Patients were assessed pre-operatively and then at 1 and 5 years post-operatively.
Results
Subject undergoing RYGB ($n=190$), AGB ($n=271$) and SG ($n=16$) were included. Estimated glomerular filtration rate (eGFR) increased following RYGB ($95+/-2$ to $101+/-1$, $P=0.01$) and AGB: $88+/-1$ to $93+/-2$, $P=0.02$). In those with eGFR <60 ml/min per 1.73 m^2 at baseline, eGFR improved over 5 years ($52+/-2$ to $68+/-7$ ml/min per 1.73 m^2, $P=0.01$). RYGB induced remission of diabetes and pre-diabetes to a greater extent than AGB (43% vs 15%; $P<0.001$). Remission of hypertension was also greater in the RYGB group at year 1 (32% vs 16%, $P=0.008$) and year 5 (23% vs 11%, $P=0.02$).
Conclusions
Bariatric surgery maintains eGFR over time. This may be due to the effect on blood pressure and glycaemia.
DOI: 10.1530/endoabs.37.GP.14.05

GP.14.06

Higher HOMA levels and failed decrease in body fat can be considered unfavourable predictors of restoring euglycaemia in diabetic cirrhotic patients undergoing liver transplantation

Valeria Grancini[1,2], Elena Lunati[1,2], Veronica Resi[1], Anna Spada[1,2] & Emanuela Orsi[1]
[1]Endocrinology and Diabetology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [2]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy.

Introduction
Diabetes mellitus (DM) is a very common complication of cirrhosis (prevalence: 20–60%), primary due to increased hepatic insulin-resistance (IR). After liver transplantation (LT), DM recovers in 67% of cases, while 33% of patients remain diabetic because of a concomitant decreased beta cell function. The roles played by pre-transplant factors determining changes in glucose tolerance after LT are imperfectly known.
Aim of the study
To highlight any factors that predict increased risk of persistence of post-transplant glucose homeostasis alterations in diabetic cirrhotic patients undergoing LT.
Materials and methods
42 patients with liver cirrhosis, 31M/11F, age 53 ± 9.9 years, underwent a metabolic and anthropometric evaluation, they underwent a bioelectrical impedance analysis (BIA) and an oral glucose tolerance test (OGTT) was performed to diagnose diabetes, before and 6 months after LT. Depending on OGTT results, patients were classified as Non Diabetic (ND) patients, who remain euglycaemic before and after LT, Diabetic (D) patients, who didn't recover from diabetes after LT, or Regressors (R), who were diabetic and returned to euglycaemia after LT. No euglycaemic cirrhotic patients became diabetic after LT, so this group was not considered. IR was assessed with HOMA index, body fat was quantified with BIA (being BMI and waist circumference unreliable in cirrhotic patients because of the presence of ascites).
Results
Depending on this classification, our population was composed by 22 ND, 13 D and seven R patients. HOMA levels before LT were higher in D patients if compared to ND and R (7.7 ± 1.7 vs 3.1 ± 0.6 and 3.7 ± 1.8 respectively, $P<0.05$).

Moreover, R showed a significant decrease in body fat, if compared to D patients ($-13.3 \pm 9\%$ vs $1.5 \pm 0.2\%$, $P<0.05$).
Conclusions
In diabetic cirrhotic patients undergoing LT, higher HOMA levels and failed decrease in body fat after LT can be considered unfavourable predictors of recovering from diabetes after transplantation.
DOI: 10.1530/endoabs.37.GP.14.06

GP.14.07

Degree of control of type 2 diabetes in Spain according to individualised glycaemic targets
Inka Miñambres[1], José Javier Mediavilla[2], Diego González-Segura[3] & Antonio Pérez[1]
[1]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [2]Centro de Salud Burgos Rural, Burgos, Spain; [3]Almirall, Barcelona, Spain.

Our objective was to estimate the distribution of Spanish diabetic patients attending to individualized glycaemic targets recommended by the ADA/EASD consensus with and without considering hypoglycaemia risk. We conducted a cross-sectional study in a Spanish primary care setting between 2011 and 2012. A total of 5382 type 2 diabetic subjects under antihyperglycaemic treatment for at least 3 months prior to inclusion completed a study visit in which clinical data including age, diabetes duration, complications and treatment, and presence of a hypoglycaemia during the last year were collected. A capillary HbA1c was measured by the A1CNow+ system. Patients were classified into different targets of HbA1c according to i) the ADA/EASD consensus without taking into account hypoglycaemia risk (presence of hypoglycaemia that required medical assistance during the past year and/or treatment with at least two insulin doses). ii) The ADA/EASD consensus taking into account hypoglycaemia risk. Mean HbA1c was 7.2 (1.2) % and 48.6% of our patients had an HbA1c $<7\%$. According to the ADA/EASD strategy without taking into account hypoglycaemia risk, 15.9, 17.1 and 67% of the patients applied to glycaemic targets of <6.5, <7 and $<8\%$ and 67.4% of the patients were considered to have an adequate glycaemic control. On the other hand, according to the ADA/EASD strategy taking into account hypoglycaemia risk 14.9, 15.5 and 69.6% of the patients applied to glycaemic targets of <6.5, <7 and $<8\%$ and 68.5% were considered to have an adequate glycaemic control. The degree of concordance between both strategies in terms of classifying patients at a certain HbA1c target was 97.4% (κ coefficient $=0.9413$).
In conclusion, individualisation of glycaemic targets increases the proportion of patients considered adequately controlled. The inclusion of information regarding hypoglycaemia risk in the ADA/EASD strategy does not affect patient classification.
Disclosure
This work was funded by grants from Almirall.
DOI: 10.1530/endoabs.37.GP.14.07

GP.14.08

Factors associated with islet yield and insulin independence after total pancreatectomy and islet cell autotransplantation in patients with chronic pancreatitis utilising off-site islet isolation: Cleveland Clinic experience
Philip C Johnston[1], Yu Lin[1], Matthew Walsh[1], Tyler Stevens[1], Rita Bottino[2], Massimo Trucco[2], James Bena[1] & Betul Hatipoglu[1]
[1]Department of Endocrinology, Diabetes and Metabolism, Cleveland Clinic, Cleveland, Ohio, USA; [2]Division of Immunogenetics, Department of Paediatrics, University of Pittsburgh, Pittsburg, Pennsylvania, USA.

Context
Total pancreatectomy (TP) with islet cell autotransplantation (IAT) can reduce or prevent diabetes by preserving β-cell function, and is normally performed with on-site isolation laboratory facilities.
Objective
We examined factors associated with islet yield and metabolic outcomes in patients with chronic pancreatitis undergoing TP-IAT. We report our experience of TP-IAT with an off-site islet isolation laboratory.
Patients and methods
Data (August 2008–February 2014) were obtained from a TP-IAT database which included information from medical records, clinic visits, questionnaires and follow-up telephone calls. Each patient was assessed with pre- and post-operative 5-h mixed meal tolerance tests for metabolic measurements and with serial HbA1c determinations.
Results
Thirty-six patients with a mean age of 38 years (range 16–72 years) underwent TP-IAT for different aetiologies. At a median follow-up time of 28 months (range 3–66), 12 patients were insulin independent and 24 patients were on at least one insulin injection a day. Post-operatively, C-peptide levels ≥ 0.3 ng/ml were present in 23/33 (70%) of the patients, with a median fasting C-peptide value of 0.8 ng/ml (range <0.2–1.5 ng/ml). Those who were insulin independent were more likely to be female ($P=0.012$), have normal morphology on pre-operative pancreatic imaging ($P=0.011$), and have significantly higher median islet yield (6845 IEQ/kg, $n=12$ vs 3333 IEQ/kg, $n=24$; $P<0.001$).
Conclusions
Islet cell autotransplantation after total pancreatectomy performed in our facility with an off-site islet isolation laboratory shows islet yield and rates of insulin independence that are comparable to other large centres with on-site laboratories.
DOI: 10.1530/endoabs.37.GP.14.08

Diabetes and obesity – basic

GP.15.01

Topical application of CD362$^+$ human mesenchymal stem cells (cyndacel-M) seeded in Excellagen scaffold augments wound healing and increases angiogenesis in a diabetic rabbit ulcer model
Swapnil Patil[1], Xizhe Chen[1], Luke Watson[2], Paul Loftus[2], Lisa O' Flynn[2], Lois Chandler[3], Gabor Rubanyi[3], Stephen Elliman[2] & Timothy O'Brien[1,4]
[1]Regenerative Medicine Institute (REMEDI) and Biosciences Research Building, National University of Ireland (NUIG), Galway, Ireland; [2]Orbsen Therapeutics, National University of Ireland, Orbsen Building, Galway, Ireland; [3]Cardium Therapeutics, San Diego, California, USA; [4]Department of Medicine, Galway University Hospital (GUH), Galway, Ireland.

Non-healing foot ulcers are a major complication in diabetic patients. Mesenchymal stem cells (MSCs) are known to promote angiogenesis with improved wound healing. Orbsen Therapeutics has identified a novel antibody (CD362$^+$) which can be used to prospectively FACS-isolate CD362$^+$CD45$^-$ MSC from human bone marrow with enhanced MSC/MNC purity ratios of up to 1/4. Excellagen matrix was used to seed the cells as biomaterials are well reported to enhance viability and therapeutic efficacy of cells. In this study, 1 million of CD362$^+$, CD362$^-$ and plastic adherent human MSCs were seeded in an Excellagen matrix and applied to cutaneous wounds in an alloxan-induced diabetic rabbit ear ulcer for a 1 week period. Statistical analysis between groups revealed that the wounds treated with an Excellagen-CD362$^+$ cell treatment demonstrated increased percentage wound closure with more prominent neovasculature. The wound sections were immunohistochemically stained by using CD31 and GSL-B4 lectins to study neovasculature. In stereological analysis, significantly increased surface density, length density and reduced radial diffusion distance was observed in the Excellagen-CD362$^+$ cell treated wound groups in comparison to untreated wounds. A subsequent study compared the beneficial effects of a combination treatment (IV delivery of cells at 2×10^6 cells/kg plus topical treatment) to topical treatment alone. A slight increase was observed in percentage wound healing in combination versus topical treated animals but this difference was not significant. There was no lowering of blood glucose levels in the combination treated animal groups over the seven day study period. Hence, with improved wound healing potential and augmenting angiogenesis, topical treatment with these specifically selected CD362$^+$ MSCs seeded in an Excellagen matrix may lead to a new therapeutic product to treat non-healing diabetic foot ulcers.
Disclosure
This research was supported by funding from EU FP7-HEALTH-2012-INNOVATION-1 grant number 305736 (REDDSTAR, Repair of Diabetic Damage by Stromal Cell Administration).
DOI: 10.1530/endoabs.37.GP.15.01

GP.15.02

Sex hormone-binding globulin protects against non-alcoholic fatty liver disease

Cristina Saez Lopez[1], Anna Barbosa-Desongles[1], Cristina Hernandez[1], Roger A Dyer[2], Sheila M Innis[2], Simo Rafael[1] & David M Selva[1]
[1]Diabetes and Metabolism Research Unit, Vall Hebron Institut de Recerca (VHIR), Universitat Autònoma de Barcelona and CIBERDEM (ISCIII), Barcelona, Spain; [2]Child and Family Research Institute, Department of Paediatrics, Faculty of Medicine, University of British Columbia, Vancouver, Canada.

Low plasma sex hormone-binding globulin (SHBG) levels are present in patients suffering chronic metabolic diseases, including non-alcoholic fatty liver disease (NAFLD). However, whether altered SHBG production plays a role in development and progression of this disease is unclear. To investigate SHBG involvement in NAFLD, we studied the effects of overexpressing SHBG in two mouse models, a genetically-induced model, by developing a double transgenic mouse by crossing the human *SHBG* transgenic mouse with the C57BL/ksJ-db/db mouse and a diet-induced model by feeding human *SHBG* transgenic mice and their WT littermates with high fructose diet (HFrD) during 8 weeks. In addition, HepG2 cells were also used to explore the molecular mechanisms involved on the SHBG role in NAFLD. Moreover, human liver biopsies were used to corroborate the *in vivo* and *in vitro* findings. The SHBG overexpression in C57BL/ksJ-db/db mice significantly reduced liver weight and liver fat accumulation by reducing lipogenesis via acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS) and ATP citrate lyase (ACLY) downregulation. Next we showed that human SHBG transgenic mice were protected against NAFLD induced by HFrD feeding that was evident in their WT littermate mice. The SHBG overexpression in this diet-induced NAFLD mouse model also reduced hepatic lipogenesis via ACC, FAS and ACLY downregulation. Furthermore, we showed a SHBG cell-autonomous effect on hepatocyte lipogenesis since SHBG overexpression reduced total triglyceride content by downregulating ACC mRNA and protein levels in HepG2 cells. Finally, the SHBG expression was inversely correlated with total triglycerides and ACC mRNA levels in human liver biopsies. Overall, we conclude that SHBG is a protective against NAFLD by inhibiting lipogenesis. Therefore, SHBG could be a new therapeutic target whereby increased expression may reduce NAFLD.

Disclosure
This work was supported by two Grants from the Instituto de Salud Carlos III (DMS) CP08/00058, PI09/144, PI12/01357 and CIBER de Diabetes y Enfermedades Metabólicas Asociadas an initiative of Instituto de Salud Carlos III (RF, ABD, CH, AL and DMS).

DOI: 10.1530/endoabs.37.GP.15.02

GP.15.03

Cardiomyopathy in the male obese diabetic db/db mice is alleviated by oxytocin treatment

Jolanta Gutkowska, Eric Plante, Ahmed Menouar, Jean-Louis Chiasson & Marek Jankowski
Department of Medicine, University of Montreal, CRCHUM, Montreal, Quebec, Canada.

Oxytocin (OT) is involved in the regulation of energy metabolism and in the activation of cardio-protective mechanisms. We evaluated whether chronic treatment with OT could prevent the metabolic and cardiac abnormalities associated with diabetes and obesity using the db/db mice model. Four-week-old male db/db mice and their lean non-diabetic littermates (db/+) serving as controls were treated with OT (125 ng/kg per h) or saline vehicle for a period of 12 weeks. Compared to db/+ mice, the saline-treated db/db mice developed obesity, hyperglycaemia and hyperinsulinaemia. These mice also exhibited a deficient cardiac OT/natriuretic peptide system and developed systolic and diastolic dysfunction resulting from cardiomyocytes hypertrophy, fibrosis and apoptosis. These abnormalities were associated with increased ROS production, inflammation and suppressed AMP-kinase signalling pathway. The male db/db mice displayed reduced serum levels of adiponectin and adipsin and elevated levels of resistin. OT treatment increased circulating plasma OT levels, significantly reduced serum resistin, body fat accumulation (19%: $P<0.001$), fasting blood glucose levels by (23%; $P<0.001$), and improved glucose tolerance and insulin sensitivity. OT also normalized cardiac OT receptors, ANP and BNP expressions and prevented systolic and diastolic dysfunction as well as cardiomyocytes hypertrophy, fibrosis and apoptosis. Furthermore, OT reduced cardiac oxidative stress and inflammation, and normalized the AMP-activated protein kinase signalling pathway. The complete normalization of cardiac structure and function by OT treatment in db/db mice contrasted with only partial improvement of hyperglycaemia and hyperinsulinaemia. These results indicate that chronic treatment with OT partially improves glucose and fat metabolism, reverses abnormal cardiac structural remodelling, preventing cardiac dysfunction in db/db mice, therefore OT plays a cardio-protective role in the diabetes.

DOI: 10.1530/endoabs.37.GP.15.03

GP.15.04

Novel human resistin antagonist (monomeric C6A mutant) reduced body weight gain and restored insulin responsiveness in mice fed high fat diet

Yacir Benomar[1,2], Gili Solomon[3], Hamza Amine[1,2], Ahlem Othmane[1,2], Arieh Gertler[3] & Mohammed Taouis[1,2]
[1]Molecular Neuroendocrinology of Food Intake,UMR 9197, University Paris Sud, ORSAY, France; [2]Molecular Neuroendocrinology of Food Intake, Neuroscience Paris-Saclay Institute, CNRS UMR 9197, University Paris Sud, ORSAY, France; [3]Faculty of Agricultural, Food and Environmental Quality Sciences, The Institute of Biochemistry, Food Science, and Nutrition, The Hebrew University of Jerusalem, Rehovot, Israel.

Resistin promotes both inflammation and insulin resistance associated with energy homeostasis impairment. Resistin is secreted by adipose tissue and macrophages, but its mechanism of action remained unknown because its receptor was not characterised. Recently, we have shown that central resistin acts by way of hypothalamic TLR4 receptors promoting overall inflammation and insulin resistance. Here, we aim to block resistin action in HFD mice that are prone to obesity and inflammation, and attempt to reverse these metabolic disorders. For this purpose, we have developed recombinant human resistin mutant (C6A) that does not form the dimeric molecule of resistin and acts as resistin antagonist (RA). The quality and purity of RA has been verified by SDS–PAGE and SEC analysis. Firstly, we tested the efficacy of RA in human neuronal cells SH-SY5Y and in mouse hypothalamic cell line. We showed that resistin (100 ng/ml) induced the phosphorylation of Akt, while RA had no such activity in both cell lines. Importantly, RA (10 mg/ml) treatment totally abolished resistin-dependent Akt phosphorylation. Once, the efficacy of RA demonstrated, we attempted to reverse the HFD-dependent insulin resistance by RA treatment *in vivo*. For this purpose, we have fed male C57BL/6 mice with HFD for 6 weeks and then mice received for 14 days daily injection of RA (0.3 mg/day per mice). We clearly show that RA leads to a significant decrease in body weight of HFD mice mainly due to loss of visceral fat. Importantly, RA treatment significantly improved both glucose tolerance and insulin responsiveness of HFD mice. Interestingly, hypothalamic IL6 expression, and reactive gliosis in the arcuate nucleus were markedly reduced in RA-treated HFD mice. Collectively, these findings indicates that the blockade of resistin action reduced body weight gain, visceral fat content and hypothalamic inflammation and restored insulin responsiveness of mice fed high fat diet.

Disclosure
This work was supported by funds from Univeristy Paris Sud and CNRS (centre national de la Recherche Scientifique), France.

DOI: 10.1530/endoabs.37.GP.15.04

GP.15.05

Stable analogues of the dual agonist dogfish glucagon show better therapeutic potential than exendin-4 in diet induced obese diabetic mice

Finbarr P M O'Harte, Ming T Ng, J Michael Conlon & Peter R Flatt
University of Ulster, Coleraine, N. Ireland, UK.

Recent acute *in vivo* studies have shown that structural modifications of dogfish glucagon improves peptide stability and these analogues can act as dual agonists at both glucagon and GLP-1 receptors. Here, we compared the effects of chronic (51 days) twice daily administration of [D-Ala^2]dogfish glucagon (Pep-N) and [D-Ala^2]dogfish glucagon-exendin-4(31–39) construct (Pep-C), exendin-4(1–39) or saline treated controls on metabolic status in groups ($4\times n=8$) of male (Swiss TO) diet induced (4 months pre-conditioned on 45% high fat diet) diabetic mice. Non-fasting blood glucose was significantly reduced in all treatment groups vs saline controls after one week and remained lower throughout the remaining study period ($P<0.05$ to $P<0.001$). Peptide therapies had no significant effect on cumulative food intake but the increase in body weight gain was lower ($P<0.05$) following Pep-N and Pep-C administration vs saline treated controls. Plasma insulin concentrations progressively increased ($P<0.05$ to $P<0.01$) in all three peptide treated groups vs high fat fed saline treated controls. After day 51, Pep-N and Pep-C showed an improved overall glycaemic response (0-120 min, area under curve AUC) to i.p. glucose (18 mmol/kg body weight) ($P<0.001$), along with exendin-4 ($P<0.05$) compared to saline treated controls. Also a significant

rise in plasma insulin concentration was noted over 120 min within all peptide treatment groups with Pep-C being the most effective insulinotropic peptide ($P<0.001$). Following chronic treatment, an insulin sensitivity test (25 U/kg body weight) showed that exendin-4 ($P<0.05$) and Pep-C ($P<0.001$) had enhanced insulin sensitivity vs saline treated controls. Terminal DEXA scan densitometry analysis revealed that percentage body fat mass was significantly decreased ($P<0.001$) in Pep-N and Pep-C treated mice but not following exendin-4 treatment. Pep-C effectively lowered plasma triglyceride concentrations ($P<0.01$). Pep-N and Pep-C caused a reduction in the terminal circulating plasma glucagon concentrations ($P<0.01$) compared to saline treated controls. Finally, pancreatic insulin content was unchanged in all of the peptide treated groups compared to saline treated control mice. In conclusion, chronic twice daily treatment with the novel dual agonist Pep-C demonstrated improved glycaemic control and lipid profiles compared with exendin-4 therapy in diet induced obese diabetic mice.

Disclosure
Invest NI (Proof of Concept) POC308 funding
PhD Studentship from DEL in N. Ireland.
DOI: 10.1530/endoabs.37.GP.15.05

GP.15.06

Activation of GPR120 by lipid agonists modulates glucagon secretion in pancreatic islets and improves glucose tolerance in mice

Noella Gormley, Peter Flatt & Aine McKillop
Ulster University, Coleraine, UK.

GPR120 is a rhodopsin-like GPCR that has a high affinity for long-chain saturated fatty acids 14–18 carbons and unsaturated fatty acids 16–22 carbons. The beneficial effects of GPR120 on β-cell function and glucose homeostasis have recently been reported however its role in glucagon secretion is unknown. GPR120 and glucagon expression were examined by double immunohistochemical studies using a glucagon secreting cell line (α-TC1.9) and pancreatic tissue from normal and high-fat fed (HFF) NIH-Swiss mice. Mechanistic and molecular studies with GPR120 agonists were used to examine alterations in intracellular Ca^{2+} and GPR120 mRNA expression in α-TC1.9 cells. Cytotoxicity was assessed by LDH release. Acute *in-vivo* effects of lipid GPR120 agonists on plasma glucose and islet hormone levels were assessed in NIH-Swiss mice. Immunocytochemistry demonstrated GPR120 co-localisation with glucagon in mouse pancreatic islets; results were confirmed in α-TC1.9 cells. Histological studies revealed that insulin was reduced ($P<0.001$) whilst glucagon ($P<0.01$) and GPR120 ($P<0.05$) expression was increased in HFF model of diabetes compared to lean controls. In mechanistic studies, endogenous GPR120 agonist DHA increased intracellular Ca^{2+} by 4.2-fold ($P<0.001$) whilst synthetic agonist GW-9508 induced a threefold increase ($P<0.05$) in α-TC1.9 cells at 5.6 mM glucose. At 16.7 mM glucose, DHA and GW-9508 augmented intracellular Ca^{2+} 5.0-fold ($P<0.01$) and 2.6-fold ($P<0.05$), respectively. No cytotoxicity was observed. PCR studies revealed that DHA increased GPR120 mRNA expression in TC1.9 cells at 5.6 mM glucose. Administration of GPR120 agonists (0.1 μmol/kg per body weight) in glucose tolerance studies was tested in NIH-Swiss mice. DHA and ALA improved glucose tolerance ($P<0.001$), augmented insulin secretion ($P<0.01$) whilst DHA reduced glucagon secretion ($P<0.001$) by 94% after 30 min. GW-9508 augmented insulin secretion ($P<0.01$) by 48% after 15 min and glucagon secretion ($P<0.001$) by 67% after 30 min. GPR120 is expressed on pancreatic alpha cells, and agonists at this receptor modulate glucagon secretion, with therapeutic potential for type-2 diabetes.

Disclosure
This work was funded by DEL.
DOI: 10.1530/endoabs.37.GP.15.06

GP.15.07

Nephroprotective properties of metformin and vildagliptin: experimental facts in type 2 diabetes

Valentina Bayrasheva[1], Elena Grineva[1,2], Alina Babenko[1,2], Yurii Dmitriev[1], Ivan Shatalov[3], Svetlana Chefu[2,1] & Alexandra Ivanova[4,5]
[1]Federal North-West Medical Research Centre, Saint-Petersburg, Russia; [2]Pavlov First St Petersburg State Medical University, Saint-Petersburg, Russia; [3]St Petersburg national research University of Information, Technologies, Mechanics and Optics, Saint-Petersburg, Russia; [4]Saint Petersburg State University, Saint-Petersburg, Russia; [5]The Komarov Botanical Institute of the Russian Academy of Sciences, Saint-Petersburg, Russia.

Background
Recent studies have demonstrated antioxidant and anti-inflammatory properties of metformin and vildagliptin, that could result in some positive effects on kidney function in diabetes. Indeed, in our previous study vildagliptin attenuated routine renal dysfunction markers in insulinopenic diabetic rats, however metformin didn't improve it. In our current study we evaluated not only glomerular dysfunction marker (albuminuria), but also novel markers of proximal tubular injury (KIM-1, NGAL) in rats with non-genetic type 2 diabetic nephropathy treated with metformin and vildagliptin.
Methods
In 3 weeks after unilateral nephrectomy adult male Wistar rats were randomly divided into diabetic group (fed high-fat diet for 5 weeks and then successively received nicotinamide (230 mg/kg) and streptozotocin (65 mg/kg) intraperitoneally) and non-diabetic group (ND) fed with normal diet and received citrate buffer without streptozotocin. Ten weeks later, diabetic animals were divided to receive either metformin (M group) 300 mg/kg per day, either vildagliptin (V group) 8 mg/kg per day, or placebo (P group) for another 10 weeks, $n=9$ each.
Results
HbA1c in diabetic groups was considerably higher compare to ND ($4.6\pm0.12\%$). At the end of the experiment vildagliptin treatment was able to considerably improve creatinine clearance (2.9 ± 0.13 ml/min per kg), and reduce urinary albumin excretion ratio (21.9 ± 1.4 mg/24 h). Even though metformin didn't attenuate routine kidney dysfunction markers such as creatinine, creatinine clearance and albuminuria (61 ± 2.9 μmol/l; 2.6 ± 0.18 ml/min per kg; 25.9 ± 4.6 mg/24 h, respectively) compared to P group (65 ± 3.6; 2.3 ± 0.21; 38.8 ± 2.5, $P\geq0.05$ each),urinary levels of KIM-1 (589 ± 93.3 ng/ml) and NGAL (1544.9 ± 100.6 pg/ml) in metformin-treated animals were significantly lower than that in diabetic rats without treatment (1097 ± 91.1; 1918.6 ± 118.1, respectively), $P<0,05$ each. Moreover, renoprotection in studying groups confirmed by morphological examination.
Conclusion
Thus, whereas vildagliptin treatment could attenuate routine markers of kidney injury, metformin has shown tubuloprotective properties without any effects on glomerular dysfunction in type 2 diabetic rats.

DOI: 10.1530/endoabs.37.GP.15.07

Diabetes and obesity – Clinical obesity and cardiovascular

GP.16.01

Suppression of plasma free fatty acid concentrations similarly reduces myocardial lipid content and left ventricular systolic function in type 2 diabetic patients and healthy controls

Peter Wolf[1], Yvonne Winhofer[1], Sabina Smajis[1], Anja Catic[1], Jürgen Harreiter[1], Lana Kosi-Trebotic[1], Siegfried Trattnig[2], Sabina Baumgartner-Parzer[1], Anton Luger[1], Martin Krssak[1,2] & Michael Krebs[1]
[1]Division of Endocrinology and Metabolism, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; [2]Department of Radiology, MR Centre of Excellence, High Field MR, Medical University of Vienna, Vienna, Austria.

Background
Metabolic inflexibility in T2DM might result in reliance on free fatty acids (FFA) as substrates to maintain myocardial energy metabolism compared to lean and healthy controls. Thus, we investigated the effects of an acute suppression of circulating FFA on myocardial lipid content and left ventricular function in extreme phenotypes.
Methods
T2DM patients (age: 56 ± 11a; BMI: 28 ± 3.5 kg/m^2; HbA1c: $7.29\pm0.88\%$) and nine healthy young controls (age: 24 ± 3a; BMI: 24 ± 3.5 kg/m^2) were investigated on two study days in random order. At baseline and at 180 min placebo or Acipimox was administered to inhibit adipose tissue lipolysis. Myocardial lipid content (MYCL) and systolic LV-function was measured by 1H-magnetic-resonance-spectroscopy and tomography at timepoints I (0–60 min), II (180–240 min) and III (420–480 min).
Results
In T2DM and controls Acipimox similarly reduced MYCL significantly (T2DM: -0.39 ± 0.07 vs CON: $-0.39\pm0.41\%$ compared to baseline), accompanied by a distinct decrease in parameters of LV systolic function without any difference between both groups (EF -13 ± 8 vs $-9\pm7\%$ compared to baseline; cardiac index: -16 ± 15 vs $-11\pm13\%$ compared with baseline; T2DM vs CON). Baseline MYCL and EF were higher in T2DM compared to controls (MYCL $0.48\pm0.12\%$ vs $0.18\pm0.01\%$; $P<0.001$; EF: $77\pm1.7\%$ vs $61\pm1.2\%$; $P<0.001$; T2DM vs CON). At baseline a strong correlation of MYCL and EF ($r=0.537$; $P<0.001$) was observed.

Discussion
Pharmacological inhibition of adipose tissue lipolysis reduces MYCL to a similar extent in T2DM and healthy controls. Thus, cardiac lipid stores might be essential for maintaining systolic heart function. These results are of clinical interest, since lipolysis-inhibiting drugs are frequently used in routine care in T2DM (insulin, nicotinic-acids).

DOI: 10.1530/endoabs.37.GP.16.01

GP.16.02

The effect of omega-3 polyunsaturated fatty acids on the arterial stiffness parameters in patients with diabetes mellitus type 2 and cardiovascular autonomic neuropathy

Victoria Serhiyenko, Volodymyr Segin & Alexandr Serhiyenko
Lviv National Medical University, Lviv, Ukraine.

Introduction
The aim of study was to analyse the effect of long-chain polyunsaturated higher ω-3 fatty acids (PUFAs) on the arterial stiffness parameters in patients with type 2 diabetes (T2DM) and cardiovascular autonomic neuropathy (CAN).
Description of methods
The study involved 39 patients with moderate CAN (55.2±3.8 years, HbA1c 7.1±0.5%. The aorta (AIxao), brachial augmentation index (AIxbr), pulse wave velocity (PWV) were assessed by TensioMedTM Arteriograph 24 (Hungary). Patients with CAN were allocated to two groups: control ($n=18$) received standart therapy and treatment ($n=21$) received in addition one capsule/day of the ω-3 PUFAs (Δ90%). The duration of the study was 3 months. Statistics: ANOVA.
Results
The arterial stiffness parameters in patients with moderate CAN exceed the physiological values, in particular AIxao +26.2% ($P<0.01$), AIxbr +66.2% ($P<0.001$), PWV +24.7% ($P<0.001$) compared to patients with T2DM without CAN. Prescription of ω-3 PUFA was accompanied by more decrease of AIxao, PWV during the 24 h, decrease of AIxao, PWV during the day and decrease of AIxao, AIxbr, PWV during the night. Simultaneously no significant influence on the AIxbr during the active period of day was not found (table).

Table

	Patients with T2DM and CAN ($n=39$)				
Parameters	Groups	Day/night	Baseline	After treatment	% change from baseline
AIxao, %	Control	Day	30.4±1.97	28.4±1.68	−4.3±4.76
		Night	33.2±1.98	30.1±1.27	−6.6±4.15
	Treatment	Day	32.0±1.32	26 4±1.12[b]	−16.2±3.12
		Night	36.6±1.65	31.7±1.23[a]	−11.2±4.2
AIxbr, %	Control	Day	−10.6±3.37	−12.0±3.11	−19.3±12.14
		Night	−4.2±2.8	−5.9±2.48	−10.0±17.23
	Treatment	Day	−9.8±2.76	−14.3±2.84	−42.8±9.0
		Night	−1.6±2.79	−10.4±3.23[a]	−98.0±18.1
PWV, m/s	Control	Day	10.2±0.4	9.6±0.4	−6.0±2.21
		Night	10.9±0.4	10.3±0.36	−4.93±1.41
	Treatment	Day	11.0±0.35	9.7±0.39[a]	−11.6±2.09
		Night	11.3±0.48	9.0±0.44[b]	−18.9±3.9

Note: The results are given as absolute values and as % change from baseline, (Δ%, Mean±SEM); [a]$P<0.05$, [b]$P<0.01$ – compared to baseline.

Conclusion
Therefore, the administration of ω-3 PUFA for 3 month promotes reduction of artery stiffness parameters in patients with T2DM and CAN.

DOI: 10.1530/endoabs.37.GP.16.02

GP.16.03

The dipeptidyl peptidase-IV inhibitor (gemigliptin) inhibits the expression of vascular adhesion molecules and inflammatory cytokines in HUVECs via Akt- and AMPK-dependent mechanisms

Ho Cheol Hong, Hwan-Jin Hwang, Hyun Jung Lee, Min Jung Lee, Ji A Seo, Sin Gon Kim, Nan Hee Kim, Kyung Mook Choi, Dong Seop Choi, Sei Hyun Baik & Hye Jin Yoo
Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University, Seoul, n/a, Republic of Korea.

Recently, dipeptidyl peptidase-IV (DPP-IV) inhibitor, a major anti-hyperglycaemic agent, has received substantial attention as a possible therapeutic target for inflammatory diseases such as atherosclerosis. However, the direct molecular mechanisms through which DPP-IV inhibitor mediates anti-inflammatory effects in vascular endothelial cells have not been clarified. The effects of the DPP-IV inhibitor, gemigliptin, were analysed in human umbilical vein endothelial cells (HUVECs) and THP-1 cells. Using western blotting, we demonstrated that gemigliptin efficiently increased the level of AMP-activated protein kinase (AMPK) and Akt phosphorylation in a dose-dependent manner. The levels of lipopolysaccharide (LPS)-mediated phosphorylated nuclear factor-κB (NF-κB) and c-Jun N-terminal kinase (JNK) were significantly decreased after gemigliptin treatment. Furthermore, gemigliptin reduced LPS-induced expression of adhesion molecules and inflammatory cytokines such as vascular cell adhesion molecule-1 (VCAM-1), E-selectin, tumour necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), interleukin-1β (IL1β), and IL6 in HUVECs. In macrophage-like THP-1 cells, gemigliptin effectively inhibited LPS- and LDL-induced foam cell formation. However, these anti-inflammatory and anti-atherosclerotic effects of gemigliptin in HUVECs and THP-1 cells were significantly reduced after treatment with an AMPK or an Akt inhibitor. Our results suggest that gemigliptin efficiently inhibited LPS-induced pro-inflammatory effects in vascular endothelial cells by attenuating NF-κB and JNK signalling via Akt/AMPK-dependent mechanisms. Therefore, the DPP-IV inhibitor, gemigliptin, may directly protect the vascular endothelium against inflammatory diseases such as atherosclerosis.
Disclosure
This study was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2012R1A1A1005257).

DOI: 10.1530/endoabs.37.GP.16.03

GP.16.04

Nocturnal blood pressure cut off points related to the development of microvascular complications and arterial hypertension in patients with type 1 diabetes

María Belén Ojeda-Schuldt[1], Isabel Mateo-Gavira[1], Francisco Javier Vilchez-López[1], Ana Montero-Galván[2], José Ortejo-Rojo[1] & Manuel Aguilar-Diosdado[1]
[1]Department of Endocrinology, University Hospital Puerta del Mar, Cádiz, Spain; [2]Nursing Unit, Department of Endocrinology. University Hospital Puerta del Mar, Cádiz, Spain.

Introduction
In preliminary results of our group, we detected an association between the mean nocturnal blood pressure and development microvascular complications. The objective was to evaluate possible nocturnal blood pressure cut off points in relation to the development or progression of retinopathy, microalbuminuria and arterial hypertension in type 1 diabetic patients.
Methods
We designed a prospective observational study of 85 patients, clinically normotensive and without microalbuminuria, monitored over 7 years. We performed a 24 h-ambulatory blood pressure monitoring (ABPM) at the beginning and after 7 years. We evaluated the development/progression of retinopathy and development of microalbuminuria and established hypertension over the follow up period. We analyzed different ranges of nocturnal systolic blood pressure (SBP) and diastolic blood pressure (DBP) as independent variables for the development of such complications
Results:
Of the 85 patients included in the analysis, 55.3% (n:47) were women with an average age of 27.9±6.1 years and a length of disease of 12.3±6.5 years. 69 patients completed 7-year study. After the follow up period, 31.8% presented development/progression of retinopathy, 10.14% developed microalbuminuria and 7.24% of the normotensive patients progressed to established hypertension. Initial nocturnal DBP greater than 65 mmHg showed as a risk factor for the progression of retinopathy and the development of hypertension after 7 years. In spite of the association between the nocturnal SBP and development of microalbuminuria, we did not detect a cut off point from which a significant risk appeared.
Conclusions
In clinically normotensive and normoalbuminuric patients with type 1 diabetes, a nocturnal DBP greater or equal to 65 mmHg is related to the development/progression of retinopathy and the development of established hypertension.

DOI: 10.1530/endoabs.37.GP.16.04

GP.16.05

Evaluation of cardiovascular risk factors in long-term survivors of brain tumours who received cranial irradiation

Nikolaos Kyriakakis[1], Satish S. Kumar[1], Julie Lynch[1], Ramzi Ajjan[2], Adam Glaser[3], Georgina Gerrard[4], Carmel Loughrey[4] & Robert D. Murray[1]
[1]Leeds Centre for Diabetes and Endocrinology, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, UK; [2]Division of Cardiovascular and Diabetes Research, Leeds Institute of Cardiovascular and Metabolic Medicine (LICAMM), University of Leeds, Leeds, UK; [3]Paediatric Haematology and Oncology, Leeds Teaching Hospitals NHS Trust, Leeds, UK; [4]Clinical Oncology, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, UK.

Introduction
There is strong evidence that adult survivors of childhood cancer have excess premature vascular morbidity and mortality, the pathophysiological mechanism of which remains unresolved.
Methods
We undertook a cross sectional study to assess cardiovascular risk in long-term survivors of brain tumours following cranial irradiation compared with healthy matched controls. The following cardiovascular markers were measured: full lipid profile, fasting glucose and parameters of body composition. Basal anterior pituitary hormone profile and dynamic pituitary tests (ITT or GST) were also undertaken in the patient group.
Results
36 patients (mean age 30.9 ± 13.9 years) and 36 controls (mean age 31.5 ± 13.4 years) were assessed. Evidence of hypopituitarism was present in 91.2% of patients (severe GHD 64.7%, partial GHD 26.5%, LH/FSH deficiency 17.6%, severe ACTH deficiency 8.8%). No significant difference was found in the TSH ($P = 0.2$) and free T_4 ($P = 0.4$) values between patients and controls. Total and LDL-cholesterol were significantly higher in patients compared with controls (5.3 ± 1.1 mmol/l vs 4.6 ± 1.0 mmol/l, $P = 0.007$ and 3.1 ± 0.8 mmol/l vs 2.7 ± 0.9 mmol/l, $P = 0.011$ respectively). Body composition analysis showed patients had significantly elevated waist circumference (93.9 ± 15.6 cm vs 80.3 ± 10.9 cm, $P < 0.001$), waist-hip ratio (0.88 ± 0.08 vs 0.82 ± 0.08, $P < 0.001$), fat mass (FM) and FM% (24.0 ± 12.2 kg vs 15.7 ± 6.6 kg, $P = 0.003$ and 29.6 ± 9.7% vs 22.1 ± 8.3%, $P < 0.001$), truncal FM and truncal FM% (13.0 ± 6.7 kg vs 8.2 ± 3.7 kg, $P = 0.004$ and 29.4 ± 10.0% vs 21.0 ± 8.1%, $P < 0.001$) and summative (suprailiac, infrascapular, biceps, triceps) skinfold thickness (75.7 ± 32.3 mm vs 42.5 ± 16.4 mm, $P < 0.001$) when compared with controls. No differences were found in the HDL, triglycerides, glucose, BMI and lean body mass between the two comparison groups.
Conclusion
Our results show that cancer survivors following cranial irradiation demonstrate an adverse lipid and body composition profile, which may contribute to the increased cardiovascular risk of these patients. The high prevalence of hypopituitarism in the patient group may explain at least partially the alterations observed in the cardiovascular risk markers.

DOI: 10.1530/endoabs.37.GP.16.05

GP.16.06

Cardiovascular complications in type 1 diabetic patients

Ines Barka, Ines Slim, Nesrine Cheikhrouhou, Koussay Ach, Yosra Hasni, Amel Maaroufi, Maha Kacem, Molka Chaieb & Larbi Chaieb
Department of Endocrinology, Sousse, Tunisia.

Background
Although the issue of cardiovascular complications in type 2 diabetic patients is widely discussed and recommendations for such screening are known, it is less common to do so for type 1 diabetes mellitus (T1DM). Unfortunately, the mortality rate due to vascular complications is higher among type 1 diabetic patients than in the general population.
Patients and methods
Seventy-six patients with T1DM history over 20 years were included in our study. We analysed the occurrence of cardiovascular complications and their risk factors: BMI, HbA1c, lipid profile, hypertension, smoking, alcohol consumption and family history of cardiovascular diseases and diabetes
Results
A total of 76 patients were enrolled: 43 men and 33 women, the mean age and the mean diabetes duration was 39.9 years ±9.5 (24–61 years) and 28.18 ± 5.9 years respectively. The HbA1c was 10.26 ± 1.76%. Smoking was present in 23.7% of our patients;hypertension was associated in 25.3 ± 4,3% and dyslipidaemia in 11.3 ± 3.18% The frequency of chronic diabetic complications was as follows: diabetic retinopathy = 75%,peripheral polyneuropathy = 55.3% and nephropathy = 28.9%. 9/76 patients had cardiovascular complications: among this group eight patients were smoker, seven had a family history of diabetes mellitus and six without nephropathy. Proven stroke was diagnosed in six patients with over 20 years of T1DM history, coronary disease and peripheral arteriopathy were present in three and two patients respectively.
Conclusion
Beyond 20 years of diabetes history, cardiovascular complications dominate the prognosis.

DOI: 10.1530/endoabs.37.GP.16.06

GP.16.07

Lipocalin-2 regulates cardiomyocyte autophagy to control apoptosis and insulin sensitivity: importance in heart failure

Hyekyoung Sung, Yee Kwan Chan & Gary Sweeney
York University, Toronto, Canada.

Lipocalin 2 has become an important biomarker for kidney disease and it is important to now understand it's role in cardiomyopathy and understand it's direct effects on the heart. Autophagy is now established as a critical determinant of cardiac function and here we investigated regulation of cardiac autophagy by lipocalin-2 and the functional consequences. After treating H9c2 cells with lipocalin-2 we used transmission electron microscopy, Western blotting and immunofluorescence for LC3-II, tandem fluorescent LC3 overexpression and MagicRed assay for lysosomal cathepsin activity to show that lipocalin-2 reduced autophagic flux. Lipocalin-2 also reduced oxidative stress in response to hypoxia. This correlated with reduced insulin sensitivity which was reversed when rapamycin was used to stimulate autophagy. We also observed that lipocalin-2 induced cardiomyocyte apoptosis. Mechanistically, we have shown that lipocalin-2 increased intracellular iron levels to mediate pro-apoptotic effects. We translated these studies to animal models by performing coronary artery ligation surgery to induce ischemia in wildtype and lipocalin-2 knockout mice. Our preliminary data indictaes that ischemia-induced caspase-3 and -12 activity was exaggerated in lipocalin-2 knockout versus wildtype. In summary, lipocalin-2 regulates cardiomyocyte autophagy, oxidative stress, apoptosis and insulin sensitivity and the exact physiological significance of these cardiac remodeling effects must now be determined.
Disclosure
Supported by a grant from Heart & Stroke Foundation of Canada

DOI: 10.1530/endoabs.37.GP.16.07

GP.16.08

Vascular and cardiac function in young adults with classical congenital adrenal hyperplasia

Joanna Wierzbicka-Chmiel[1], Artur Chmiel[2], Dariusz Kajdaniuk[1,3] & Bogdan Marek[1,3]
[1]Department of Endocrinology and Diabetology, Rybnik, Silesia, Poland; [2]Department of Cardiology, Rybnik, Silesia, Poland; [3]Division of Pathophysiology, Department of Pathophysiology and Endocrinology, Silesian Medical University, Zabrze, Poland.

Background
The patients with classical congenital adrenal hyperplasia (CAH) have increased cardiovascular risk due to the lifelong glucocorticoid therapy and the disease per se.
Objective
To evaluate vascular and cardiac function in adults with CAH during optimal corticosteroid and fludrocortisone replacement therapy.
Patients and methods
Cross-sectional study of 19 adults with CAH (age 23.7 years ±3.8; males 63%) compared to 21 healthy voluntaries (age 23.2 years ±2.6; males 60%) matching to the age and BMI. All of the participants had assessed the flow mediated

dilatation of the brachial artery (FMD), the intima-media thickness of the common carotid artery (CIMT), the intima-media thickness of the common femoral artery (FIMT), the left ventricular ejection fraction (LVEF%), left ventricular mass index (LVMI) and longitudinal left ventricular function using two-dimensional speckle-tracking echocardiography (LSTE). Classical cardiovascular risk factors and hormones status were also measured.
Results
The patients with CAH compared with controls have decreased FMD (mean FMD% 9.4, 95% CI: 7.2–11.6 vs mean 19.8, 95% CI: 17.7–21.9; $P<0.01$) and the difference was still significant after correction for potential confounders such as: brachial artery diameter, age, sex, the dose of corticosteroid and fludrocortisone (mean FMD% after correction 9.2, 95% CI: 4.2–14.3 vs 20.0, 95% CI: 15.2–24.9; $P=0.02$). The CIMT and FIMT was higher in the CAH group baseline (for CIMT mean 0.47 mm, 95% CI: 0.46–0.49 vs mean 0.40 mm, 95% CI: 0.38–0.42; $P<0,001$, for FIMT mean 0.47 mm, 95% CI: 0.45–0.48 vs mean 0.41 mm 95% CI: 0.38–0.42; $P<0.001$) but not after correction for potential confounders such as: age, sex, the dose of corticosteroid and fludrocortisone, total cholesterol level, smoking status (for CIMT $P=0.44$, for FIMT $P=0.12$). The CAH subjects compared with controls have normal and similar LVEF%, LVMI. The mean absolute value of LSTE differs in the CAH patients compared with controls (20.9%, 95% CI: 20.2–21.6 vs 21.9%, 95% CI: 21.2–22.5; $P=0.03$).
Conclusions
Young adults with CAH have impaired endothelial function but the increased of IMT may be related to hormones supplementation. In addition patients with CAH have impaired left ventricular function in two-dimensional speckle-tracking echocardiography.

DOI: 10.1530/endoabs.37.GP.16.08

Pituitary – Neuroendocrinology and central salt regulation

GP.17.01

Retinoic acid increases glucocorticoid receptor phosphorylation via cyclin-dependent kinase 5

Hélène Roumes[1], Julie Brossaud[1,2], Aloïs Lemelletier[1], Marie-Pierre Moisan[1], Véronique Pallet[1], Anabelle Redonnet[1] & Jean-Benoît Corcuff[1,2]
[1]UMR1286 INRA Univ Bordeaux, Bordeaux, France; [2]University hospital, Bordeaux, France.

Background
According to the literature, glucocorticoid receptor (GR) function is modulated by phosphorylation. Retinoic acid (RA) can activate some cytoplasmic kinases able to phosphorylate GR.
Aim
As RA and glucocorticoids interact in neuronal cells, we investigated whether RA could modulate GR phosphorylation in such cells.
Methods
HT-22 hippocampal cells were cultured 4d with or without dexamethasone (Dex, 10-6 M) or RA (10-6 M). Western blots were either performed on total cell extracts or cytosolic and nuclear fractions.
Results
Indeed, a 4 d treatment by RA decreased the nuclear expression of GR phosphorylated on Serine 220 (pSer220GR). Conversely, RA increased Dex-dependent nuclear pSer220GR expression in HT22 cells. This treatment by RA had no effect on cyclin-dependent kinase 5 (CDK5) expression but increased the expression of p35 a major CDK5 cofactor. In the nucleus, roscovitine, a CDK5 inhibitor, suppressed the RA-dependent increase of the Dex-induced pSer220GR expression. Furthermore, roscovitine altered RA-dependent decrease of GR-induced transcriptional activity when using either a reporter gene with GR response elements or GR sensitive genes such as BDNF or tissue transglutaminase.
Conclusion
This study demonstrates that RA modulates GC signalling by increasing Ser220GR phosphorylation through at least a modulation of CDK5/p35 activity with an increase of cytoplasmic p35/p25 ratio. This study supports the idea that GR phosphorylation depends on the cellular environment aside from the presence of GR ligands.
Disclosure
This study was supported by the Conseil Régional d'Aquitaine and the University of Bordeaux1.

DOI: 10.1530/endoabs.37.GP.17.01

GP.17.02

Glp-1 regulates the reproductive function and synchronizes the onset of the puberty in female rats

Veronica Outeiriño Iglesias[1,2], Marina Romaní Perez[3], Juan Fandiño Gómez[1,2], Lucas Carmelo González Matías[1,2], Federico Mallo Ferrer[1,2] & Eva María Vigo Gago[1,2]
[1]Faculty of Biology. University of Vigo, Vigo (Pontevedra), Spain; [2]Group of Endocrinology and Neurophysiology, Biomedical Research Center (Cinbio), University of Vigo, Vigo (Pontevedra), Spain; [3]Nutrineuro, Universitè of Bordeaux, Inra, Bordeaux (Aquitaine), France.

GLP-1 is a gut hormones with insulinotropic effects. GLP-1 is expressed at the hypothalamus having regulatory functions in food intake and neuroendocrine corticoadrenal axis (HPA). Energy balance and HPA have deep influence in the gonadal function of mammals. Exendin-4 (Ex4) is a potent agonist for the GLP-1 receptor.
Objectives
To evaluate the effects of native GLP-1 (7–36)-NH2(GLP-1) and Ex4 in the function of the reproductive system in adulthood and onset of puberty in female rats.
Methods
Adult female rats were *i*cv injected with a single dose of GLP-1/Ex4 or vehicle (Veh) in the morning of proestrous. Blood samples were taken by jugular venipuncture at different stages of the subsequent estrous cycle. Ovaries were isolated for histological studies. Another group of females was housed with males for mating that confirmed by sperm-positive vaginal plug. The dams were sacrificed by decapitation after delivery, and number of undelivered but implanted fetuses and neonates born were counted and weighed. Prepubertal rats were treatment with GLP-1/Ex4/Veh and monitoring of body weight, intake, vaginal opening (VO) and hormone levels was done.
Results
GLP-1 administration in the morning of proestrus doubled the amplitude of preovulatory LH surge and modified the estradiol and progesterone levels along the estrous cycle. That promoted a marked increase in number of Graafian follicles and corpora lutea, and consequently in litter size. Conversely, Ex4 produced a partial blockade of preovulatory LH surge, yet not affecting the number of mature follicles or corpora lutea. Administration of low doses of GLP-1 to pre-pubertal rats synchronized vaginal opening and increased LH levels. By contrast, chronic exposure to Exendin-4 produced a significant reduction in LH and complete blockade of puberty onset.
Conclusions
GLP-1 increases the preovulatory surge of gonadotropins and ovulation rate in adulthood and synchronise the onset of puberty. These effects were not reproduced by Ex4.
Disclosure
This work was supported by a grant from the Ministerio de Ciencia e Innovación, Spain (BFU 2011-27790).

DOI: 10.1530/endoabs.37.GP.17.02

GP.17.03

Insulin-induced hypoglycaemia decreases IGF1 bioactivity in humans: a missing link to increased mortality in diabetic patients?

Zeinab Sarem[1,2], Biruhalem Assefa[1,3], Martin O Weickert[4,5], Aikatarini Adamidou[1], Jan Frystyk[6], Matthias Möhlig[1], Stefanie Lieske[2], Andreas L Birkenfeld[1,2], A.F.H Pfeiffer[1,2], Joachim Spranger[1,7] & Ayman M Arafat[1,2]
[1]Department of Endocrinology, Diabetes and Nutrition, Charité-University Medicine Berlin, Berlin, Germany; [2]Department of Clinical Nutrition, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany; [3]Department of Endocrinology, Diabetes and Nutrition at the Center for Cardiovascular Research (CCR), Charité-University Medicine Berlin, Berlin, Germany; [4]Warwickshire Institute for the Study of Diabetes, Endocrinology and Metabolism,University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK; [5]Division of Metabolic & vascular Health, Warwick Medical School, University of Warwick, Coventry, UK; [6]Medical Research Laboratories, Institute of Clinical Medicine, Faculty of Health Sciences, Aarhus University, DK-8000 Aarhus C, Aahrus, Denmark; [7]Department of Endocrinology, Diabetes and Nutrition at the Experimental and Clinical Research Center (ECRC), Charité-University Medicine Berlin and Max-Delbrück Centre Berlin-Buch,, Berlin, Germany; [8]Section of Metabolic Vascular Medicine,Medical Clinic III, University Clinic Dresden, Dresden, Germany.

Background
The mechanisms underlying the association between severe hypoglycaemia and increased cardiovascular mortality among patients with diabetes mellitus are not

fully understood. Our aim was to evaluate changes in GH/IGF1 axis during insulin-induced hypoglycaemia, as a possible link.
Methods
Twenty-five healthy subjects, 12 obese participants (OP; 6/ 6; 34.4 ± 1.7 kg/m^2), and 13 healthy lean participants (LP; 6/ 7; 21.7 ± 0.6 kg/m^2) were studied using insulin tolerance test and changes in GH, total IGF1, IGF binding proteins (IGFBPs) and IGF1 bioactivity, measured by the cell-based KIRA method, were investigated. Moreover, the effect of insulin on mRNA expression of parts of the GH/IGF1 system was further studied in mouse primary hepatocytes.
Results
Under hypoglycaemic conditions, insulin significantly increased IGFBP2 and decreased IGF1 bioactivity in both groups ($P < 0.01$). This was followed by a surge in GH ($P < 0.01$). As expected, insulin decreased IGFBP1 levels, whereas no changes in total IGF1 and IGFBP3 levels were observed. *In vitro*, insulin stimulation of primary hepatocytes lead to a decrease of IGFBP1 and IGFBP3 and increase of IGFBP2 mRNA expression.
Conclusion
The insulin-induced hypoglycaemia is associated with a decrease in IGF1 bioactivity through up-regulation of IGFBP2. Our results point to a possible and previously poorly explored mechanism explaining the strong association between hypoglycaemia and increased cardiovascular mortality among diabetic patients.
DOI: 10.1530/endoabs.37.GP.17.03

GP.17.04

Copeptin reflects thermal strain during exercise in a hot environment
Mike Stacey[1,2], David Woods[2,3], Stephen Brett[1,4], Simon Delves[5], Sophie Britland Britland[5], Joanna Fallowfield[5] & Adrian Allsopp[5]
[1]Imperial College, London, UK, [2]Royal Centre for Defence Medicine, Birmingham, UK; [3]Carnegie Faculty Leeds Beckett University, Leeds, UK; [4]Hammersmith Hospital, London, UK, [5]Institute of Naval Medicine, Alverstoke, Hants, UK.

Background
Exertional heat illness (EHI) is an incapacitating and sometimes fatal phenomenon. It is associated with elevated core temperature (Tc), cardiovascular instability and the systemic inflammatory response syndrome. EHI-preventive guidelines recommend maintaining Tc ≤38 °C, an important thermoregulatory threshold above which vasomotor compensation plateaus and pronounced excursions in key pituitary and adrenal hormones occur. Copeptin, the C-terminal part of the vasopressin (AVP) precursor peptide, can be assayed as a surrogate for AVP. Copeptin shows prognostic potential in a range of inflammatory and cardiovascular conditions but its relationship with Tc has not been characterised.
Objective
To investigate the serum copeptin response to Tc changes during exercise in a hot environment.
Methods
15 subjects from a British Army infantry battalion were studied on their sixth day in Kenya during a 4.5 h simulated combat assault exercise. Tc was recorded by telemetry from ingested pills every 60 s during the exercise. Serum copeptin was assayed pre- and post-exercise.
Results
Tc increased in 15/15 subjects. Average Tc (TcAv) was 37.36 ± 0.21 °C. Change in plasma copeptin concentration (Δcopeptin) was positive in 13/15 subjects. Mean Δcopeptin was 6.67 ± 5.83 pmol/l ($P = 0.0006$). In eight subjects with maximum Tc (TcMax) >38 °C, mean Δcopeptin was more than 400% greater than for the seven subjects with TcMax <38 °C (10.40 ± 4.34 pmol/l vs 2.40 ± 4.2 pmol/l; $P = 0.0059$). There was a strong positive correlation between TcAv and Δcopeptin ($r = 0.75$, $P < 0.01$).
Conclusions
Copeptin stratified military subjects relative to the critical thermal threshold of 38 °C. Copeptin may be a plausible biomarker of thermal strain and EHI risk in both military and civilian populations.
Disclosure
This work was supported by the Surgeon General, Headquarters Defence Medical Services and the Royal Navy Fleet Command
DOI: 10.1530/endoabs.37.GP.17.04

GP.17.05

Hypernatremia and copeptin levels in the elderly hospitalised patient
Gabriel Munter[1,2], Michal Liber[1,2] & Moshe Sonnenblick[1,2]
[1]Shaare Zedek Medical Center, Jerusalem, Israel; [2]Hadassah Medical School-Hebrew University, Jerusalem, Israel.

Introduction/objective
Elderly patients have a higher prevalence of hypernatremia. Previous studies suggested that impaired ADH secretion contributes to development of hypernatremia in the elderly. Copeptin is the C terminal part of the ADH precursor and is more stable in plasma than ADH. The aim of this study was to detect demographic and clinical characteristics of the elderly hypernatremic patient hospitalized in the internal medicine ward, and to increase the understanding of the role of ADH secretion in the pathogenesis of hypernatremia.
Design
Case–control study.
Setting
Internal Medicine ward in a University affiliated hospital.
Participants
/33 hypernatremic patients (admission sodium >150 meq/l, age >70) compared to 34 normonatremic patients.
Measurements
Demographic, functional and clinical data (APACHE II score) were collected at admission. Serum copeptin levels were obtained 48 hours from admission. Mortality and change in the functional status were followed up to 30 days after discharge.
Results
Patients with hypernatremia presented with significantly lower baseline functional and cognitive states and higher APACHE II score (21.3 ± 8.6 vs 15.4 ± 6.7, $P < 0.01$). Dementia was present in 97% of the hypernatremic patients compared to 46% of the control group ($P < 0.001$). Mortality within 30 days of discharge was higher in the hypernatremic group (58% vs 32%, $P < 0.05$). Higher Copeptin levels were found in the hypernatremic group compared to the normonatremic group (100.2 ± 60.6 pmol/l v. 66.5 ± 57.2 pmol/l, $P < 0.05$). High levels of Copeptin were associated with higher in hospital ($P < 0.05$) and 30 days mortality ($P < 0.01$). Sodium levels were found to correlate with Copeptin levels; yet, an even stronger correlation was demonstrated between Copeptin levels and Apache II score ($r = 0.52$, $P < 0.001$).
Conclusions
Hypernatremia in the elderly at admission is associated with a high rate of mortality. Copeptin is appropriately secreted by the elderly patient with dementia and seems to be a good single disease severity marker.
Disclosure
Mirski fund.
DOI: 10.1530/endoabs.37.GP.17.05

GP.17.06

Predictors of response to fluid restriction in hyponatremic patients due to the syndrome of inappropriate antidiuresis
Sophia Lengsfeld[1,3], Bettina Winzeler[1,4], Nicole Nigro[1,4], Isabelle Suter-Widmer[1,4], Philipp Schütz[2,4], Birsen Arici[1,4], Martina Bally[2,4], Claudine Blum[2,4], Andreas Bock[4,5], Andreas Huber[2,6], Beat Müller[2,4] & Mirjam Christ-Crain[1,4]
[1]Division of Endocrinology, Diabetes and Metabolism, Department of Internal Medicine, University Hospital Basel, Basel, Switzerland; [2]Medical University Clinic, Division of Endocrinology, Diabetology and Metabolism, Kantonsspital Aarau, Aarau, Switzerland; [3]Division of Emergency Medicine, Department of Internal Medicine, University Hospital Basel, Basel, Switzerland; [4]Department of Clinical Research, University Hospital Basel, Basel, Switzerland; [5]Division of Nephrology, Dialysis and Transplantation, Department of Internal Medicine, Kantonsspital Aarau, Aarau, Switzerland; [6]Institute of Laboratory Medicine, Kantonsspital Aarau, Aarau, Switzerland.

Introduction
Fluid restriction (FR) is often the recommended first-line treatment for hyponatremia due to the syndrome of inappropriate antidiuresis (SIAD). However, FR not always leads to successful correction of hyponatremia, making predictive markers of treatment response desirable. The aim of this study was to

evaluate routinely measured laboratory parameters, copeptin and pro-atrial natriuretic peptide (pro-ANP) as possible predictors of treatment success to FR.
Methods and design
We analysed 106 patients with SIAD out of 298 prospectively observed patients with profound hyponatremia (serum sodium <125 mmol/l). 82/106 patients with SIAD were initially treated with FR and included in this study. FR was defined as a total daily intake of <1000 ml. According to the change from baseline to follow-up serum sodium (within 24 h), we classified patients into FR responders (increase of >3 mmol/l) or FR non-responders (≤ 3 mmol/l). We performed regression models to look for correlations between different urine and serum parameters and treatment response.
Results
Of the 82 patients (mean age 67.6 years, 64.6% females) 48 (58.5%) responded to the initial trial of FR. Both baseline levels of urinary sodium and u-osmolality showed a significant correlation with treatment response (P for interaction $=0.004$ and $P=0.041$ respectively), whereat high levels indicate a FR failure. Initial serum sodium did not predict response to FR ($P=0.26$). Similarly, levels of copeptin – a surrogate marker of arginine vasopressin (AVP) – did not reveal a significant correlation with treatment success ($P=0.68$). Finally, we found a predictive value of pro-ANP; the higher pro-ANP levels the greater the likelihood of a positive response (P for interaction $=0.004$).
Conclusion
Easy measured urinary parameters and pro-ANP correlate with therapeutic success of fluid restriction and may enhance the management of patients with hyponatremia due to SIAD.
Disclosure
Thermo Scientific Biomarkers provided all the kits for measurement of Copeptin and MR-proANP analysis. P Schütz, B Müller, and M Christ-Crain have received speaker honoraria from Thermo Scientific Biomarkers. N Nigro was supported by a grant from the University Basel, Switzerland.

DOI: 10.1530/endoabs.37.GP.17.06

GP.17.07

Heterogenous patterns of recovery from adipsic diabetes insipidus in adult patients

Martin Cuesta Hernandez, Rosemary Dineen, Saket Gupta, Ridhwaan Salehmohamed & Christopher Thompson
Academic Department of Endocrinology, Beaumont Hospital, Dublin, Ireland.

Introduction
The natural history of adipsic diabetes insipidus (ADI) is not completely understood. Isolated case reports suggest occasional recovery of adipsia. We present the follow up of a cohort of 12 patients with ADI.
Setting
National pituitary unit with interest in diabetes insipidus.
Methods
ADI was identified by demonstrating absent thirst and AVP responses to hypertonic saline infusion. Results 12 patients with ADI were identified (fivecraniopharyngioma, four ACOM aneurysm repair, one congenital, one neurosarcoidosis, and one prolactinoma). Three patients died. Six patients had permanent adipsic diabetes insipidus. Three patients had recovery of thirst, with a heterogenous pattern of recovery.
Case 1: A 41-year-old female with an intrasellar craniopharyngioma developed postoperative ADI with persistent hypernatremia (147–172 mmol/l). Two years postoperatively, she complained of thirst, and hypertonic saline infusion showed normal thirst but absent AVP responses, confirming recovery of thirst with persistent DI.
Case 2: A 29-year-old Caucasian had craniotomy and radiotherapy for craniopharyngioma which had previously presented with chronic headache and bitemporal hemianopia and developed ADI postoperatively. Eight years post-op, she presented with thirst, seizures and pNa of 112 mmol/l. Hypertonic saline infusion showed persistent DI but thirst responses typical of compulsive water drinking; she has had recurrent hyponatraemia since then.
Case 3: A 51-year-old gentleman developed ADI after clipping of an ACOM aneurysm and was treated with desmopressin and sliding fluid scale. 10 years post surgery; he sensed the return of thirst; repeated hypertonic saline infusion showed recovery of both thirst and AVP secretion. He is asymptomatic off desmopressin.
Conclusion
We report that three out of 12 patients with ADI recovered thirst after longstanding adipsia. The pattern of recovery was heterogenous and included complete recovery of ADI, recovery of adipsia only and conversion of adipsia to polydipsia. Both the mortality of 25% and the recovery rate of 25% should be considered during long-term surveillance.

DOI: 10.1530/endoabs.37.GP.17.07

GP.17.08

A study of hyponatraemia in acute medical admissions

Heidy Hendra[1], Fiona Graham[1], Christine Catley[1], Tatjana Boitsova[1], Tamer Rezk[1], Suki Sankaralingam[2] & Sumith Abeygunasekara[1]
[1]Renal Unit, Chelmsford, Essex, UK; [2]Clinical Chemistry, Chelmford, Essex, UK.

Introduction
Hyponatraemia is the commonest electrolyte disorder in clinical practice and is closely associated with increased morbidity, mortality and length of hospital stay. It can be classified into mild (124–134 mmol/l), moderate (115–124 mmol/l), and severe (<115 mmol/l). The aim of the study was to determine the prevalence, aetiology, and management of hyponatraemia in general hospital.
Methods
A total of 4139 acute medical admissions were studied. Hyponatraemia was found in 536 patients with 441 being mild, 86 moderate and nine severe; 130 cases were analysed further in details.
Results
Out of 130 cases; 86 were of mild (66%), 42 moderate (32%), and one severe hyponatraemia (0.8%). The mean age was 75.1 years (17–99) and there is equal male to female ratio. The cause of hyponatraemia was only identified in 68% with diuretics accounting for 41 (46%), Syndrome of Inappropriate ADH Secretion (SIADH) for 36 (40%) and fluid overload for 12 (9%) of cases. The treatment of hyponatraemia included intravenous fluid resuscitation in 52, cessation of diuretics in 43 and fluid restriction in 48 of cases. One subject with severe hyponatraemia received demeclocycline, none of the subjects received hypertonic saline or Vasopressin receptor antagonist. While the average length of stay for all medical admissions was 4 days, the average length of stay is 17.1 days (2–70) in those with hyponatraemia.
Conclusion
Hyponatraemia, which presents in 12.9% of our admissions, is associated with significantly prolonged hospital length of stay. The use of diuretics and SIADH were the main cause of hyponatraemia in our cohort. Our study highlighted the challenge in the diagnosis as evidenced by 32% of patients in whom diagnosis was not reached. A trust guideline has been developed as a response to this issue.

DOI: 10.1530/endoabs.GP.17.08

GP.17.09

The dopastatin BIM-23A760 distinctly influences key functional endpoints in different types of pituitary adenomas and normal pituitaries: role of somatostatin and dopamine receptor profile

Justo P Castaño[1], Alejandro Ibáñez-Costa[1], Laura M López-Sánchez[1,2], Manuel D Gahete[1], Esther Rivero-Cortés[1], Mari Carmen Vázquez-Borrego[1], María Ángeles Gálvez[3], Andrés de la Riva[4], Eva Venegas-Moreno[5], Luis Jiménez-Reina[6], Alberto Moreno-Carazo[7], Francisco José Tinahones[8], Silvia Maraver-Selfa[8], Miguel A Japón[9], Juan Antonio García-Arnés[10], Alfonso Soto-Moreno[5], Susan M Webb[11], Rhonda D Kineman[12], Michael D Culler[13] & Raúl M Luque[1]
[1]Department of Cell Biology, Physiology and Immunology, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Hospital Universitario Reina Sofia, CIBER Fisiopatolo, University of Cordoba, Córdoba, Spain; [2]Research Unit, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Hospital Universitario Reina Sofia, University of Cordoba, Córdoba, Spain; [3]Service of Endocrinology and Nutrition, Hospital Universitario Reina Sofia, Instituto Maimónides de Investigación Biomédica de Córdoba, Córdoba, Spain; [4]Service of Neurosurgery, Hospital Universitario Reina Sofia, Córdoba, Spain; [5]Metabolism and Nutrition Unit, Instituto de Biomedicina de Sevilla (IBIS), Hospital Universitario Virgen del Rocío, Sevilla, Spain; [6]Department of Morphological Sciences, University of Cordoba, Córdoba, Spain; [7]Endocrinology and Nutrition Unit, Complejo Hospitalario de Jaén, Jaén, Spain; [8]Service of Endocrinology and Nutrition, Hospital Clínico Universitario Virgen de la Victoria, Málaga, Spain; [9]Department of Pathology, Hospital Universitario Virgen del Rocío, Sevilla, Spain; [10]Department of Endocrinology and Nutrition, Carlos Haya Hospital, Málaga, Spain; [11]Department of Endocrinology, Centre for Biomedical Research on Rare Diseases (Centro de Investigación Biomédica en Red de Enfermedades Raras Unit 747), Hospital Sant Pau, Autonomous University of Barcelona, Barcelona, Spain; [12]Research and Development Division, Department of Medicine, Jesse Brown Veterans Affairs Medical Center, University of Illinois at Chicago, Chicago, Illinois, USA; [13]IPSEN Bioscience, Cambridge, Massachusetts, USA.

Chimeric somatostatin (SST)/dopamine (DA) compounds, termed dopastatins, such as BIM-23A760, an agonist for SST (sst2 and ss5) and DA (D2) receptors, are emerging as promising new approaches to treat pituitary adenomas. However, their actions and mechanisms on the different types of pituitary tumours are still incompletely understood. Thus, the aim of this study was to analyse a set of key functional parameters (signaling pathways, hormonal expression and secretion, cell viability, and apoptosis), in response to BIM-23A760 in a series of 74 human pituitary tumors: 22 somatotropinomas, five mixed GH/PRL-secreting adenomas, 11 corticotropinomas, 26 NFPAs, six prolactinomas, one FSH-secreting gonadotropinoma and three TSH-omas; and in five normal human pituitaries and pituitary samples derived from three female olive baboons (*Papio anubis*). Although, BIM-23A760 has recently been withdrawn from clinical development after finding that a dopaminergic metabolite accumulates and interferes with the activity of the parent compound *in vivo*, it is still considered a good prototype molecule for dopastatins, and the results generated herein might be indeed useful in understanding and predicting the response to this type of compounds, which may be used for clinical purposes in the future. Our results demonstrate that BIM-23A760 differentially impacted all functional parameters analysed, with most responses being clearly inhibitory for cell signalling, hormone secretion and cell survival. Yet, interestingly, certain pituitary adenomas displayed distinct, even opposite responses to BIM-23A760 (i.e. paradoxical stimulatory responses), which were associated with the relative expression levels of SST- and DA-receptors. In particular, alterations on the expression of sst5 and its truncated variant, sst5TMD4, might represent potential molecular signatures contributing to the differential, inhibitory/stimulatory response to BIM-23A760 in GH- and ACTH-secreting adenomas. Altogether, our results reinforce the notion that chimeric dopastatins (e.g. BIM-23A760) can affect multiple, clinically relevant parameters on most types of pituitary adenomas and may represent new therapeutic tools to treat pituitary tumours, wherein the relative SST/DA receptor expression profile might provide useful molecular markers to predict the ultimate response of these tumours to BIM-23A760.

Disclosure
This work was supported by Junta de Andalucía (CTS-1406, BIO-0139, PI-0639-2012) Ministerio de Economía y Competitividad, Gobierno de España (BFU2013-43282-R), Instituto de Salud Carlos III (PI13/00651), Centro de Investigación Biomédica en Red de la Fisiopatología de la Obesidad y Nutrición (CIBERobn) and Ayuda Merck Serono 2013. M D Culler is an employee of IPSEN.

DOI: 10.1530/endoabs.GP.17.09

Pituitary – Basic and IGF-1

GP.18.01

Chronic stress decreases circulating endocannabinoid 2-arachidonoylglycerol in healthy human subjects

Buqing Yi[1], Igor Nichiporuk[2], Matthias Feuerecker[1], Gustav Schelling[1] & Alexander Choukèr[1]
[1]Hospital of the University of Munich (LMU), Munich, Germany; [2]Institute for Biomedical Problems, Moscow, Russia.

Increasing evidence indicates chronic stress plays an important role in a variety of health problems such as the development of autoimmune disease, and the results from mice studies suggest that the central endocannabinoid (eCB) system regulates endocrine and neuronal responses to stress. However, it is unclear how the eCB system responds to chronic stress in healthy humans. A 520-day isolation-and-confinement study simulating an interplanetary spaceflight mission to Mars provided an extraordinary chance to study the effects of chronic stress imposed by prolonged isolation. Six healthy males participated in this mission and stayed in the simulated spacecraft for 520 days. The current study aimed to investigate the effects of chronic stress on circulating concentrations of eCBs in these healthy subjects. Blood samples for eCBs measurements were obtained before and at regular intervals during the isolation period. Salivary samples were taken for cortisol assay. 24 h urine samples were collected for catecholamines measurements. Blood concentrations of the eCBs, N-arachidonylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG), were determined. Compared with the baseline level, stress hormone cortisol levels and urine norepinephrine secretions were significantly increased during the isolation period, indicating a stressed condition. Interestingly, stress decreased blood concentrations of 2-AG, but not AEA. Furthermore, 2-AG concentrations were negatively correlated with salivary cortisol levels. These results indicate that chronic stress decreases circulating 2-AG in healthy human subjects, suggesting dysregulation of 2-AG signalling is specifically implicated in humans under chronic stress.

Disclosure
This study was supported by grants from the German Ministry of Technology and Economics (BMWi as handled by DLR) (grant numbers 50WB0919 and 50WB1317).

DOI: 10.1530/endoabs.GP.18.01

GP.18.02

Neuroactive steroids as predictive markers for Alzheimer's disease

Marketa Vankova[1], Daniela Vejrazkova[1], Petra Lukasova[1], Olga Bradnova[1], Gabriela Vacinova[1], Katerina Dvorakova[1], Martin Hill[1], Josef Vcelak[1], Robert Rusina[2], Iva Holmerova[3] & Bela Bendlova[1]
[1]Institute of Endocrinology, Prague, Czech Republic; [2]Thomayer Hospital, Prague, Czech Republic; [3]Faculty of Humanities, Charles University, Prague, Czech Republic.

Background and aims
Neuroactive steroids and their metabolites play an important regulatory role in the nervous system affecting the neuronal plasticity, stress response, learning, and memory. The aim of the study was to compare the steroid metabolome in AD patients and controls.
Materials and methods
The study comprised of 48 AD patients (30 women and 18 men; age 73.8±9.54 years) and 33 matched controls (22 women and 11 men; age 68.2±5.94 years). All subjects underwent neuropsychological examination and magnetic resonance imaging of the brain. Biochemical characterisation included examination of fasting glucose and lipid metabolism and the determination of extended spectrum of steroid hormones by GC–MS method (38 steroids and their sulfates). Statistical analyzes were performed using Statgraphics Centurion XVI 16.0.07 Software.
Results
AD patients had significantly higher insulin secretion (fasting insulin, HOMAF) and lower C peptide/insulin ratio compared to controls which indicates the decreased hepatic insulin extraction. AD patients had higher C21 steroids (5β-pregnane-3α, 20α-diol conjugate, women in addition pregnenolone, 16α-hydroxy-pregnenolone, 16a-hydroxy-progesterone, men in addition 16α-hydroxy-DHEA, and pregnanolone) and lower C19 steroids (5α-androstan-3β, 17β-diol conjugate, women in addition conjugates of androsterone, epiandrosterone, epietiocholanolon, and 5β-androstane-3β, 17β-diol) compared to controls. Neither in AD nor in controls a direct relationship of steroids with fasting glucose, insulin and HOMAR was found.
Conclusion
C21 steroid levels were consistently higher in AD, suggesting an increased activity of the zona fasciculata of adrenal gland. Conversely, levels of stable 5α/β reduced catabolites of C19 steroids, particularly their sulfates, are consistently reduced in AD (unlike insignificantly different unreduced androgenic precursors showing a diurnal variation). This indicates a decrease in the activity of the adrenal zona reticularis in AD. AD patients have higher levels of insulin in the periphery, however, the direct relationship between glucose tolerance and steroid metabolome was not confirmed.

Disclosure
This work was supported by grant IGA MH CR NT13543-4, MH CR 00023761.

DOI: 10.1530/endoabs.GP.18.02

GP.18.03

Regulation of sexually dimorphic growth of murine skeletal muscle by Stat5a and Stat5b

Ryan Paul[1,2], Marianne Elston[1], John Conaglen[1] & Chris McMahon[2]
[1]Department of Medicine, Waikato Clinical School, University of Auckland, Hamilton, New Zealand; [2]AgResearch, Ruakura, New Zealand.

GH regulates IGF1 predominantly through the intracellular signallers Stat5a and Stat5b. Inactivating mutations of Stat5b in humans result in severe growth retardation and low circulating IGF1 concentrations in males and females. In mice, however, there is only a loss of sexually dimorphic growth in males when Stat5b is deleted. No study has observed Stat5b$^{-/-}$ mice beyond 12 weeks or investigated any subsequent changes in skeletal muscle mass or IGF1 expression. Blood and hindlimb muscles of male and female Stat5b$^{-/-}$ mice and WT littermates were collected at 6, 12, and 24 weeks of age ($n=16$/time and sex). Plasma IGF1 and IGF1 protein concentrations were determined by ELISA and muscle mass was normalised to bone length. C2C12 myoblast cell lines were treated with viral Stat5b siRNA and/or Stat5a siRNA or a scrambled vector (control), then differentiated and treated with GH (100 ng/ml) for 24 h. RNA was harvested for quantitative PCR. The treated cell lines were also treated for 96 h with GH (100 ng/ml) and differentiation was assessed by immunocytochemistry. Sexual dimorphism was reduced, but persisted in Stat5b$^{-/-}$ mice. Nasoanal length, tibia length and normalised hindlimb muscle mass were decreased to a greater extent in male (23%) than in female (14%) Stat5b$^{-/-}$ mice at all ages ($P<0.001$). Concentrations of IGF1 in plasma and skeletal muscle were significantly reduced in male Stat5b$^{-/-}$ mice at all ages and in female Stat5b$^{-/-}$ mice at 6 weeks. Stat5a knockdown inhibited myotube differentiation (36%) to a lesser extent than Stat5b or dual Stat5a/5b knockdown (80%) ($P<0.001$). Either Stat5a or Stat5b knockdown prevented the GH-induced myotube hypertrophy, but only Stat5a knockdown blocked the upregulation of IGF1 mRNA by GH. We conclude that both Stat5a and Stat5b have independent roles in GH signaling in murine skeletal muscle.

Disclosure
Waikato Medical Research Foundation (grant number 223).

DOI: 10.1530/endoabs.37.GP.18.03

GP.18.04

A small hypothalamic volume correlates with impaired cognitive outcome in childhood onset craniopharyngioma on long-term follow up

Sigridur Fjalldal[1], Cecilia Follin[1], Sanaz Gabery[2], Åsa Petersén[2], Lars Rylander[3], Bertil Ekman[4], Aki Johansson[5], Kai Österberg[3], Magdalena Jansson[5], Andrea Rovira[5] & Eva-Marie Erfurth[1]
[1]Department of Endocrinology, Skåne University Hospital, Lund, Sweden; [2]Translational Neuroendocrine Research Unit, Department of Experimental Medical Science, Lund University, Lund, Sweden; [3]Division of Occupational and Environmental Medicine, Lund University, Lund, Sweden; [4]Department of Medical and Health Sciences, Linköping University, Linköping, Sweden; [5]Institution of Psychology, Lund University, Lund, Sweden.

Background
Hypothalamic damage caused by craniopharyngioma (CP) is related to memory deficits, disturbed attention, and impaired processing speed. This is the first study that aims to establish a structure to function relationship by assessing cognitive function in adult patients with childhood-onset (CO) CP along with volumetric analysis of the hypothalamus.
Method
Forty-one (24 women) surgically treated CO-CP patients (median age at diagnosis; 11 years) from the South Medical Region of Sweden were included in the study. Eighteen patients had received cranial radiotherapy. Twenty-eight patients had panhypopituitarism, 35 were treated with ADH and 32 with GH. Time since first operation was 23 years (range 4–49) and median age at investigation was 35 years. Hypothalamic damage was found in 23 patients. All subjects were examined with a battery of cognitive tests and 35 patients underwent magnetic resonance imaging (MRI). A novel delineation procedure based on T1-weighted MRI and landmarks used in histologically processed postmortem hypothalamic tissue was used to estimate hypothalamic volume. Comparisons were made with 32 healthy matched controls.
Results
CP patients with hypothalamic damage ($n=23$) had lower cognitive performance pertaining to vocabulary ($P=0.02$) short term memory ($P=0.04$ and $P=0.01$), spatial ability ($P=0.02$), and executive functions ($P=0.01$ and $P=0.02$). A significantly positive correlation was found between the tests of vocabulary ($r=0.352$, $P=0.04$) and short term memory ($r=0.354$, $P=0.04$), ($r=0.357$, $P=0.04$) and hypothalamic volume.
Conclusion
Adults with hypothalamic damage due to CO-CP have impaired memory, spatial ability and executive function. Patients with smaller hypothalamic volume have worse cognitive outcome. To be able to preserve hypothalamic function we need tailored surgical and radiation strategies. Long-term follow up should include training programs pertaining to impaired cognitive function.

Disclosure
The Swedish Children's Cancer Foundation, the Medical Faculty, Lund University, Sweden.

DOI: 10.1530/endoabs.37.GP.18.04

GP.18.05

Presence and functional actions of In1-ghrelin splicing variant reveals a potentially relevant pathophysiological role in human pituitary adenomas

Alejandro Ibáñez-Costa[1], Manuel D Gahete[1], Esther Rivero-Cortés[1], David Rincón-Fernández[1], Richard Nelson[2], Manuel Beltrán[3], Andrés de la Riva[4], Miguel A Japón[5], Eva Venegas-Moreno[6], María Ángeles Gálvez[7], Juan A García-Arnés[8], Alfonso Soto-Moreno[6], Jennifer Morgan[2], Natia Tsomaia[2], Michael D Culler[2], Carlos Dieguez[9], Justo P Castaño[1] & Raúl M Luque[1]
[1]Department of Cell Biology, Physiology and Immunology, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Hospital Universitario Reina Sofia, University of Cordoba, CIBER Fisiopatolo, Córdoba, Spain; [2]IPSEN Bioscience, Cambridge, Massachusetts, USA; [3]Department of Pathology, Puerta del Mar University Hospital, Cádiz, Spain; [4]Service of Neurosurgery, Hospital Universitario Reina Sofia, Córdoba, Spain; [5]Department of Pathology, Hospital Universitario Virgen del Rocío, Sevilla, Spain; [6]Metabolism and Nutrition Unit, Instituto de Biomedicina de Sevilla (IBIS), Hospital Universitario Virgen del Rocío, Sevilla, Spain; [7]Service of Endocrinology and Nutrition, Instituto Maimónides de Investigación Biomédica de Córdoba, Hospital Universitario Reina Sofia, Córdoba, Spain; [8]Department of Endocrinology and Nutrition, Carlos Haya Hospital, Málaga, Spain; [9]Department of Physiology, University of Santiago de Compostela, CIBER Fisiopatología de la Obesidad y Nutrición, Santiago de Compostela, Spain.

Pituitary adenomas comprise a heterogeneous group of tumours causing serious comorbidities, which would benefit from identification of novel, common molecular/cellular biomarkers and therapeutic targets. The ghrelin system comprises a complex molecular family with multiple functions, and some of its components have been linked to development of various endocrine-related cancers. In this work we aim at better delineating the patho-physiological significance of the ghrelin regulatory system in pituitary tumours, by pursuing two specific objectives: i) to analyse the presence in pituitary tumours of key components of the ghrelin system: native-ghrelin, the recently discovered splicing variant In1-ghrelin, ghrelin receptors GHS-R1a (full-length) and GHS-R1b (truncated variant), and MBOAT4 (GOAT), the enzyme responsible for ghrelin acylation and ii) to compare the direct effects of native-ghrelin and In1-ghrelin variant administration on selected functional parameters in cell cultures derived from the main types of pituitary adenomas. To this end, we studied a large series of 180 pituitary samples: 76 somatotropinomas, 57 non-functioning pituitary adenomas, 29 corticotropinomas, seven prolactinomas, and 11 normal pituitary samples. The results obtained revealed that expression pattern of ghrelin system components undergoes a striking alteration in pituitary adenomas, as compared with normal pituitary, particularly In1-ghrelin, which was consistently over-expressed in all human pituitary adenoma subtypes. Interestingly, similar to that observed for native-ghrelin, In1-ghrelin was functionally active in cultured pituitary adenoma cells, as it increased GH and ACTH secretion, Ca^{2+} and ERK1/2 signalling, and cell viability, being the effects of In1-ghrelin variants generally greater than those evoked by native-ghrelin. Finally, overexpression of In1-ghrelin (by transfection using an specific expression plasmid) increased cell viability, while the use of a specific siRNA for this ghrelin variant reduced cell viability. Altogether, our results indicate that ghrelin system components are present and markedly altered in human pituitary tumours, where In1-ghrelin variant, particularly, could play a relevant functional role in the regulation of adenoma pathology, this paving the way for using In1-ghrelin variant as a new tool to explore novel diagnostic/prognostic biomarkers and/or therapeutic targets in these human tumours.

Disclosure
This work was supported by Junta de Andalucía (CTS-1406, BIO-0139, PI-0639-2012) Ministerio de Economía y Competitividad, Gobierno de España (BFU2013-43282-R), Instituto de Salud Carlos III (PI13/00651), Centro de Investigación Biomédica en Red de la Fisiopatología de la Obesidad y Nutrición

(CIBERobn) and Ayuda Merck Serono 2013. R Nelson, J Morgan, N Tsomaia, and M D Culler are employees of IPSEN.

DOI: 10.1530/endoabs.37.GP.18.05

GP.18.06

Comparison of high-throughput platforms in evaluation of whole genome miRNA expression profiles in pituitary tissues

Henriett Butz[1], Otto Darvasi[2], Peter M Szabo[1], Istvan Liko[2], Lorinc Pongor[2], Sandor Czirjak[3], Karoly Racz[1,4] & Attila Patocs[2]
[1]Molecular Medicine Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest, Hungary; [2]'Lendület' Hereditary Endocrine Tumors Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest, Hungary; [3]National Institute of Neurosurgery, Budapest, Hungary; [4]2nd Department of Medicine, Faculty of Medicine, Semmelweis University, Budapest, Hungary.

Introduction
There are three principal high-throughput methods that have been widely used to determine whole genome miRNAs expression profiles: i) microarrays, ii) qPCR based arrays, and iii) next generation sequencing (NGS). Our aim was to compare the results obtained from these platforms in normal and adenomatous pituitary samples and to validate the results by an independent sample set using qPCR.
Material and methods
Using four normal pituitary (NP) and eight non-functioning pituitary adenoma (NFPA) samples we determined miRNA expression profile by GeneChip microRNA Galaxy Array v1, SOLiD NGS and qPCR based TaqMan Low Density Array Card (TLDA). For biological confirmation expression of 22 miRNAs by individual TaqMan assays on additional 24 NFPAs and ten NPs was used as validation cohort.
Results
Totally 848 miRNAs of which only 162 were detected by all three approaches. Significant but not strong correlations between microarray and NGS (R^2: 0.471 and 0.220; $P<0.01$), microarray and TLDA (R^2: 0.462 and 0.339; $P<0.01$), and NGS and TLDA (R^2: 0.353 and 0.290; $P<0.01$) were detected in NFPAs and NPs respectively. Various bioinformatics, including commercially available software CLCbio, free, web based (Bowtie) and one our own algorithms were used in order to test whether the different evaluation of NGS data would affect the correlations. Correlations between different bioinformatical approaches were strong (R^2: 0.96–0.99) suggesting that these algorithms are useful and give similar results. Biological validation showed that 81% of TLDA results, and 72% of both microarray and NGS results could be validated regarding the direction of expression changes.
Conclusion
miRNA expression profiles measured by different platforms showed poor correlation and they were hardly comparable. Consequently, selection of screening method can influence experimental results obtained by analyses using high-throughput data (e.g. pathway analysis). However, individual miRNA expression from microarrays and NGS results were replicable in an acceptable percentage by qPCR.
Disclosure
KTIA-201200010.

DOI: 10.1530/endoabs.37.GP.18.06

GP.18.07

The hypothyroidism alters circadian clock expression in anterior pituitary gland

Paula Bargi-Souza, Rodrigo A Peliciari-Garcia, Rafael Maso Prévide & Maria Tereza Nunes
Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil.

The anterior pituitary gland occupies a central position in the hypothalamus–pituitary glands axes and secretes hormones involved in reproduction, growth, and metabolism. The plasma concentrations of pituitary hormones present fluctuations during the 24 h and are markedly altered during the hypothyroidism. The presence of an intra-pituitary circadian oscillator might be related to these oscillations; however, the molecular mechanism and the consequences of the hypothyroidism are still unknown. The purpose of the present study was to investigate the expression of *Bmal1, Per2*, *Dbp*, *Nr1d1*, *Rora*, and *Dio2* in pituitary during the adult hypothyroidism. For this, euthyroid and thyroidectomized (Tx) male Wistar rats were euthanized during 24 h, every 6 h. The pituitaries were excised and the mRNA expression was evaluated by RT-qPCR. *Gapdh* and *Rpl19* were used as internal control. One and two-way ANOVA, as well as, cosinor analysis were used to evaluate the time-of-day-dependent differential expression for each gene/group and their interactions. The expression of *Bmal1*, *Per2*, *Dbp*, *Nr1d1*, *Rora*, and *Dio2* presented a circadian pattern in anterior pituitary of euthyroid rats and the peak of *Per2*, *Dpb*, *Rora*, and *Dio2* expression occurred at ZT 12, while for Bmal1 was ZT 0/24. In the hypothyroid animals, the circadian pattern of *Bmal1*, *Rora*, and *Dio2* was lost and the acrophase of *Per2*, *Dbp*, and *Nr1d1* was advanced about 2.5 h, 3 h, and 45 min respectively. Tx also reduced Mesor values of *Dbp* and *Nr1d1*. Our studies reveal that the expression of core clock and clock-controlled genes in anterior pituitary gland are changed during the hypothyroidism and might contribute directly or indirectly to the altered hormonal pattern of secretion observed in this pathological condition. Further studies are in progress to assess this issue.
Disclosure
This work was supported by the FAPESP (2013/05629-4).

DOI: 10.1530/endoabs.37.GP.18.07

GP.18.08

Role of miR-375 in oncogenesis of pituitary adenomas

Laura Sanchez-Tejada[5], Ruth Sanchez-Ortiga[1], Pedro Riesgo[8], Javier Abarca[6], Carmen Fajardo[3], Irene Monjas[7], Rosa Cámara[4], Cristina Lamas[2] & Antonio Picó[1]
[1]Endocrinology Department, Hospital General Universitario Alicante, Alicante, Spain; [2]Endocrinology Department, Hospital General Universitario Albacete, Albacete, Spain; [3]Endocrinology Department, Hospital La Ribera, Alzira, Spain; [4]Endocrinology Department, Hospital Universitario La Fe, Valencia, Spain; [5]Research Unit, Hospital General Universitario Alicante, Alicante, Spain; [6]Neurosurgery Department, Hospital General Universitario Alicante, Alicante, Spain; [7]Otorhinolaryngology Department, Hospital General Universitario Alicante, Alicante, Spain; [8]Neurosurgery Department, Hospital La Ribera, Alzira, Spain.

Purpose
MicroRNAs (miRNAs) are a fundamental component of gene regulation mechanisms. Presently, altered miRNA patterns of expression have been documented in different human cancers, and they may explain the distinct behavior of pituitary adenomas (PA) and the differences between subtypes. miR-375 can target among other genes to IGF1 receptor (IGF1R) and participes in reprogramming cancer cell metabolism. The aim of this study was to assess the miR-375 role on pathogenesis of different PA subtypes.
Methods
In this cross-sectional descriptive study, we evaluated miR-375 by qRT-PCR analysis on 60 human PA samples: 29 gonadotrophs (GT), 15 somatotrophs (ST), eight functioning corticotroph (CT), and eight silent corticotroph adenomas (SCA). Nine healthy pituitary from autopsies were used as calibrator reference. Aggressiveness was graded according to invasiveness (Hardy's grade IV) and Ki-67 gene expression (>2.59 fold change (FC)).
Results
In our whole sample miR-375 was associated with sex (men: 3.00 (1.63–4.36) FC values vs women: 1.35 (0.47–1.92) FC values, $P=0.002$) and was positively correlated with age ($r=0.466$, $P=0.000$). miR-375 expression patterns differed depending on PA subtype ($P=0.000$) and non functioning PA (GT and SCA) revealed overexpression compared with functioning PA (CT and ST) (81.3 (26/37) vs 39.3 (11/23)), entailed a risk of 6.7 (2.1–21.5) times higher ($P=0.001$). Its expression was also correlated with tumor maximum diameter ($r=0.303$, $P=0.022$) and associated with their extension (intrasellar: 1.05 (0.47–1.47); extrasellar: 2.50 (1.47–4.39); and invasive: 2.50 (1.07–3.88); $P=0.008$). In addition, 66.7% tumors with high or medium aggressiveness grades overexpressed miR-375 vs 28.6% with low grade, which entailed a risk 5.0 (1.6–16.0) times higher ($P=0.005$).
Conclusion
Our results revealed a different role for miR-375 in the pathogenesis of PA depending on subtype. This miRNA may be a marker of aggressiveness, but further studies are needed for endorse this utility.
Disclosure
This work was supported by FISABIO (FCVI-HGUA-2012-C01).

DOI: 10.1530/endoabs.37.GP.18.08

GP.18.09

Molecular classification of pituitary adenomas

Antonio Picó[1], Laura Sanchez-Tejada[5], Ruth Sanchez-Ortiga[1], Rosa Cámara[4], Cristina Lamas[2], Javier Abarca[6], Irene Monjas[7], Pedro Riesgo[8] & Carmen Fajardo[3]
[1]Endocrinology Department, Hospital General Universitario Alicante, Alicante, Spain; [2]Endocrinology Department, Hospital General Universitario Albacete, Albacete, Spain; [3]Endocrinology Department, Hospital La Ribera, Alzira, Spain; [4]Endocrinology Department, Hospital Universitario La Fe, Valencia, Spain; [5]Research Unit, Hospital General Universitario Alicante, Alicante, Spain; [6]Neurosurgery Department, Hospital General Universitario Alicante, Alicante, Spain; [7]Otorhinolaryngology Department, Hospital General Universitario Alicante, Alicante, Spain; [8]Neurosurgery Department, Hospital La Ribera, Alzira, Spain.

Purpose
The 2004 edition of the WHO text 'Histological typing of endocrine tumors' classified pituitary adenomas (PA) on the basis of their histological and immunohistochemical characteristics. Recent advances on the knowledge of the molecular patterns of these tumours may allow establishing a molecular classification with higher accuracy and specificity than previous one.
Methods
Within the pale of the multicenter Spanish Molecular Registry of Pituitary Adenomas (REMAH), a multicentre clinical-basic project, we had obtained the molecular phenotype of 172 PA. Expression levels of 26 genes were measured by qRT-PCR, including all pituitary hormones, receptors for somatostatin, dopamine, and others: GH-releasing hormone receptor, gonadotropin-releasing hormone receptor, type 1 corticotropin-releasing hormone receptor, arginine vasopressin receptor 1b and type 1 ghrelin receptor, and three housekeeping genes for normalization. Nine healthy pituitary from autopsies were used as calibrator reference.
Results
Based on the established clinical diagnosis (functioning PA (FPA: somatotroph, corticotroph, tirotroph, and lactotroph adenomas) and non-functioning PA (NFPA)) and immunohistochemical data, we have defined ranges of expression for all hormones and receptors with 25th and 75th percentiles for each subtype. NFPA and FPA presenting expression of several hormonal genes were subclassified depending on the dominant expression, establishing as 'gold standard' the p25 expression in the complete sample. On the basis of our study we have been able to define the following molecular classification: somatotroph (pure, mixed, and plurihormonal), functioning corticotroph, tirotroph, lactotroph, gonadotroph (FSHoma, LHoma, and mixed), null cell, and silent corticotroph adenomas with higher accuracy than the immunohistochemical previous classification.
Conclusion
Advances in the molecular knowledge of the pathogenesis of PA may allow a more specific classification of PA, especially in the case of NFPA, helping physicians to better manage these patients.
Disclosure
This work was supported by SEEN (Novartis–REMAH).
DOI: 10.1530/endoabs.37.GP.18.09

Pituitary – Acromegaly

GP.19.01

Coagulation parameters and platelet function analysis in patients with acromegaly

Hamiyet Yilmaz Yasar[1], Mustafa Demirpence[1], Ayfer Colak[1], Banu Ozturk Ceyhan[2], Yusuf Temel[1], Nese Simsek[1], Ismail Karademirci[1] & Umit Bozkurt[1]
[1]Tepecik Research and Training Hospital, Izmir, Turkey; [2]Aydin Medline Hospital, Izmir, Turkey.

Objective
Acromegaly is associated with increased cardiovascular morbidity and mortality. But the data about the evaluation of coagulation and fibrinolysis in acromegalic patients is very limited and to our knowledge, platelet function analysis has never been investigated. So we aimed to investigate the levels of protein C, protein S, fibrinogen, antithrombin 3, and platelet function analysis in patients with acromegaly.
Methods
Thirty-nine patients with active acromegaly and 35 healthy subjects were included in the study. Plasma glucose and lipid profile, fibrinojen levels, GH, and IGF1 levels and protein C, protein S, and antithrombin III activities were measured in all study subjects. Also, platelet function analysis was evaluated with collagen/ADP- and collagen–epinephrine-closure times.
Results
Demographic characteristics of the patient and the control were similar. As expected, fasting blood glucose levels and serum GH and IGF1 levels were significantly higher in the patient group compared with the control group (pglc: 0.002, pGH: 0.006, and pIGF1: 0.001 respectively). But lipid parameters were similar between the two groups. While serum fibrinogen and antithrombin III levels were found to be significantly higher in acromegaly group (pfibrinojen: 0.005 and pantithrombin III: 0.001), protein S and protein C activity values were signicantly lower in the patient group (protein S: 0.001 and protein C: 0.001). Also, significantly enhanced platelet function (measured by collagen/ADP- and collagen/epineprine-closure times) was demonstrated in acromegaly (pcol-ADP: 0.002 and pcolepineprine: 0.002). There was a negative correlation between serum GH levels and protein S (r: −0.25, P: 0.04) and protein C (r: −0.26, P: 0.04) values. Likewise, there was a negative correlation between IGF1 levels and protein C values (r: −0.39, P: 0.002), protein S values (r: −0,39, P: 0.001), collagen/ADP-closure times (r: −0.28, P: 0.02), and collagen/epineprine-closure times (r: −0.26, P: 0.04). Also we observed a positive correlation between IGF1 levels and fibrinogen levels (r: 0.31, P: 0.01).
Conclusion
Acromegaly was found to be associated with increased tendency to coagulation and enhanced platelet activity. However, with the treatment of IGF1 hypersecretion, these changes in haemostatic parameters could be possibly controlled.
DOI: 10.1530/endoabs.37.GP.19.01

GP.19.02

Assessment of bone quality, measured by trabecular bone score, in acromegaly

Elena Malchiodi[1,2], Elisa Sala[1,2], Elisa Verrua[1], Elisa Cairoli[1,2], Giulia Carosi[1,2], Emanuele Ferrante[2], Marcello Filopanti[2], Fabio Massimo Ulivieri[3], Cristina Eller-Vainicher[2], Iacopo Chiodini[1,2], Giovanna Mantovani[1,2] & Anna Spada[1,2]
[1]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; [2]Endocrinology and Diabetology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [3]Nuclear Medicine Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

Introduction
Acromegaly is characterised by chronic exposure to high GH and IGF1 levels that leads to increased bone turnover. Regardless of BMD value, acromegalic patients seem to have an increased vertebral fracture risk probably due to a reduction of bone quality. Trabecular bone score (TBS) is a new index used for assessing bone microarchitecture. In this study TBS was used for the first time to analyze bone quality in acromegaly.
Methods
16 new acromegalic patients (12F, age 56.3±13.8, BMI 28.1±6.3) and 16 controls matched for age, gender, menopausal state, and BMI were enrolled. Patients with MEN1, ectopic GHRH secretion, and history of secondary osteoporosis were excluded. All participants underwent lumbar radiograph and dualenergy X-ray absorptiometry scan on lumbar spine (LS) and femur (total:FT and neck:FN). TBS was assessed in the region of LS-BMD.
Results
56% of patients had a macroadenoma, 18% had hypopituitarism (all hypoadrenalism), and nobody had cosecretion. BMDs were not different between the two groups (acromegalic patients vs controls: LS T-score −0.5±1.3 vs −0.7±1.0, P=0.7 and LS Z-score 0.5±1.3 vs 0.5±1.5, P=0.7; FN T-score −0.6±0.9 vs −0.7±1.2, P=0.8 and FN Z-score 0.3±0.7 vs 0.2±0.8, P=0.4; FT T-score 0.02±1.01 vs −0.5±0.99, P=0.2 and FT Z-score 0.64±0.84 vs 0.4±0.8, P=0.4) while acromegalic patients had lower TBS than controls (TBS Z-score −2.27±2.05 vs −1.00±0.9, P=0.04 and TBS value 1.195±0.14 vs 0.8±0.6, P=0.01). Two patients and one control had vertebral fractures (P=1.0). In acromegalic patients, at bivariate analysis TBS was associated with age at diagnosis (r^2: −0.25, P=0.04), GH serum levels (r^2: 0.36, P=0.01), FN T-score (r^2: 0.35, P=0.02), and Z-score (r^2: 0.81, P=0.01). Vertebral fractures were

associated with age at diagnosis (r^2: 0.36, $P=0.02$). LS-BMD and FT-BMD were related to alteration of glucose metabolism (r^2: 0.25, $P=0.04$ and r^2: 0.49, $P=0.002$ respectively).
Conclusions
Acromegalic patients had impaired bone quality despite normal bone density. Further larger studies are needed to define TBS role in fracture risk in acromegaly.
DOI: 10.1530/endoabs.37.GP.19.02

GP.19.03

Perceived quality of life in acromegaly: results from a tertiary UK centre

Nikolaos Kyriakakis[1], Julie Lynch[1], Stephen G Gilbey[1], Susan M Webb[2] & Robert D Murray[1]
[1]Leeds Teaching Hospitals NHS Trust, Leeds Centre for Diabetes and Endocrinology, St James's University Hospital, Leeds, UK; [2]Biomedical Research Institute Sant Pau (IIB Sant Pau), Hospital de Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain.

Introduction
Patients with acromegaly are frequently left with long-term adverse sequelae. When compared with individuals with other pituitary adenomas, patients with acromegaly demonstrate greater impairment in their quality of life (QoL).
Methods
The disease-specific questionnaire, AcroQoL, and the generic psychological general well-being schedule (PGWBS) were used to evaluate QoL in an acromegaly patient cohort. Longitudinal data were also collected to determine change in QoL over a 5-year period.
Results
Baseline responses were collected from 58 patients (age 55.1 ± 13.0 years). For the entire cohort, mean GH and IGF1 values at baseline were 1.53 ± 2.07 μg/l and 102.1 ± 51% of the upper limit of normal (ULN) respectively. Mean duration of GH control (GH <2 μg/l) was 5.4 ± 4.8 years, whereas for IGF1 this was 4.4 ± 4.3 years. Follow-up responses were obtained from 23 patients (age 55.6 ± 10.0 years). For this subgroup, mean GH and IGF1 at follow-up were 0.76 ± 0.75 μg/l and 110.4 ± 54.3% of ULN respectively (vs 1.6 ± 2.4 μg/l and 110.5 ± 64.7% of ULN at baseline). The mean total score for AcroQoL at baseline was 67.8 ± 18.4 (48.0%). The domain of appearance was the most under-marked, while the highest scores were noted in the personal relationships domain. For the subgroup of 23 patients, no significant difference was found in the baseline and follow-up AcroQoL scores (64.2 vs 65.7, $P=0.58$). PGWBS scores were significantly lower in the patient group compared with reference population, both at baseline (median score 71.5 (IQR 52.0–86.5) vs 89.5 (IQR 81.0–95.75), $P<0.001$) and follow-up (median score 61.0 (IQR 46.0–83.0) vs 89.5 (IQR 81.0–95.75), $P<0.001$). Baseline and follow-up PGWBS scores were not statistically different for the subgroup of 23 patients. Positive well-being, general health and vitality were the mostly under-marked domains.
Conclusion
Our results demonstrate impairment of QoL in acromegaly, which fails to improve despite long-term disease control. A more holistic approach, potentially in a multi-disciplinary setting involving clinical psychologists, should be implemented.
DOI: 10.1530/endoabs.37.GP.19.03

GP.19.04

Molecular and pathological determinants of somatostatin analogue resistance: somatotropinomas in AIP mutated and X-LAG syndrome patients

Misu Lee[1], Adrian Daly[2], Liliya Rostomyan[1], Natalia Pellegata[2] & Albert Beckers[1]
[1]Institute of Pathology, Helmholtz Zentrum München, Munich, Germany; [2]Department of Endocrinology, CHU de Liège, University of Liège, Liège, Belgium.

Poor hormonal and tumour responses to somatostatin analogues (SSA) in acromegaly can occur although the aetiology is often unclear. Two genetic syndromes are associated with relative SSA resistance: acromegaly due to AIP mutations (AIPmut) and the newly described X-linked acrogigantism (X-LAG) syndrome due to chromosome Xq26.3 microduplications. We studied whether SSA resistance in these conditions was related to somatostatin receptor (SSTR) levels in tumour tissues. We studied six XLAG and seven AIPmut patients, none of which had hormonal control on chronic SSA therapy, and ten mutation-negative patients (controls). Immunostains were evaluated semi-quantitatively and an immunoreactive score (IRS) was recorded for each section. Staining was assessed as negative for IRS 0–1, weakly positive for IRS 2–3, moderately positive for IRS 4–8, and strongly positive for IRS >8. In AIPmut cases, one was negative for SSTR2, two for SSTR5 and three for SSTR1. SSTR3 was the most highly expressed receptor in both acromegaly controls (average IRS 9.8) and in AIPmut (average IRS 9.5) somatotropinomas. SSTR1 and SSTR5 were present at higher levels in the controls vs AIPmut cases. The difference between AIPmut and controls was statistically significant for SSTR1 ($P=0.039$) but not for SSTR5 ($P=0.239$). Interestingly, the expression level of SSTR2 was significantly higher in the control somatotropinomas (average IRS 7.9) compared with the AIPmut (average IRS 2.3) adenomas ($P=0.0026$). Furthermore, in the AIPmut somatotropinomas, six out of seven samples had SSTR2 IRS scores <3, while in controls only three out of 13 had SSTR2 IRS <3. In XLAG syndrome cases, SSTR2 and SSTR3 were expressed in all samples analyzed, while one was negative for SSTR1, and another was negative for SSTR5. We observed that the expression of SSTR2 was variable but moderate to high in all cases (IRSs 4–10), despite the poor to absent SSA responses. SSTR3 was also highly expressed (average IRS 8.8) in the analyzed XLAG tumours, while the levels of SSTR1 and SSTR5 were lower than that of SSTR2 in these cases. Despite both having poor responses to SSA, variable expression of SSTR2 occurs in AIPmut and XLAG syndrome somatotropinomas. SSTR3 appears to be highly expressed in somatotropinomas, irrespective of the genetic background.
Disclosure
This work was supported by Pfizer.
DOI: 10.1530/endoabs.37.GP.19.04

GP.19.05

Clinical and biochemical outcomes during pregnancy in patients with acromegaly

Triona O'Shea[1], Saket Guptha[1], Audrey Melvin[2], Karen McGurran[1], Ruth Casey[2], Donal O'Halloran[2], James Gibney[3], Christopher Thompson[1] & Mark Sherlock[3]
[1]Beaumont Hospital, Dublin 9, Ireland; [2]Cork University Hospital, Cork, Ireland; [3]Tallaght Hospital, Dublin, Ireland.

Acromegaly is a rare condition resulting from excess secretion of GH and IGF1. Acromegaly is frequently associated with subfertility. As such there is little data on the course of the disease during pregnancy, and of the effects of the disease and its treatments on the foetus.
Objective
We describe known pregnancies in women with acromegaly within the Republic of Ireland over a 15-year period.
Methods
We collected clinical, biochemical, and outcome data during and following pregnancy.
Results
We have identified 11 pregnancies in eight women. All women had a pituitary macroadenoma. In eight cases there was concurrent prolactin hypersecretion. Ten out of 11 patients were medically treated prior to conception. Dopamine agonists were most commonly used (8/11) followed by somatostatin analogues (4/11). One patient was treated with both dopamine agonists and somatostatin analogues. In 7/11 cases dopamine agonist therapy was continued throughout the pregnancy. Median IGF1 at conception was 240% above the upper limit of the age related reference range (IQR 230–380%). At the time of conception 2/11 cases had IGF1 levels within the age related reference range. During the third trimester IGF1 was within the reference range in 6/10 cases, and in all cases IGF1 levels fell during pregnancy. One patient was treated for hypertension throughout two pregnancies. No patient developed diabetes mellitus or any neurological complications during pregnancy. All babies were delivered via elective Caesarean section at term. Four babies were breastfed post delivery. Mean birth weight was 2.8 kg, with no cases of macro- or microsomia.
Conclusions
Our data suggests that pregnancy in acromegalic women is not associated with excess morbidity to mother or baby. There is a high rate of Caesarean section. Our data correlates with previous studies showing a beneficial effect of pregnancy on biochemical control of acromegaly.
DOI: 10.1530/endoabs.37.GP.19.05

GP.19.06

Criteria for disease control in acromegaly under SSA treatment: mean GH profile or GH random?

Nunzia Prencipe, Chiara Bona, Joannis Karamouzis, Alessandro Maria Berton, Stellina Valentina Di Giacomo, Federica Guaraldi, Ezio Ghigo & Silvia Grottoli
Endocrinology, Diabetology and Metabolism, AOU Città della Salute e della Scienza of Turin, University of Turin, Turin, Italy.

Acromegaly is due to increased GH secretion usually sustained by a GH-secreting pituitary adenoma. Somatostatin analogues (SSA) can control GH hypersecretion in 60% of patients and tumor volume in 30%. The disease control is, in turn, associated with lower mortality and therefore to verify the optimal control of the disease activity is of critical importance to adapt the dose and the choice of alternative treatment. The criteria for optimized disease control had been assumed as mean GH <2.5 ng/ml and normal for age IGF1 levels. In 2010 a consensus proposed as new criteria GH random (GHR) <1 ng/ml and normal for age IGF1 levels. We compared the reliability of mean GH profile (GHP) <2.5 and GHR <1 ng/dl as good marker of disease activity in acromegaly; we also evaluated the association between GH levels (mean and random) and IGF1/IGFBP3 levels. To this goal in an observational and retrospective study, we enrolled 34 responsive to SSA treatment acromegalic patients (25F, 33–86 years). The clinical response had been defined by normal IGF1 levels and no clinical activity. In all subjects the dose of SSA had been stable in last 2–5 years. In all subjects in phase 1 (before 2010) mean GHP, IGF1, and IGFBP3 and in phase 2 (after 2010) GHR, IGF1, and IGFBP3 had been evaluated. In all subjects in both phases of the study IGF1 (phase 1: 186.8 ± 10.0 and phase 2: 175.0 ± 37.3) and IGFBP3 (phase 1: 2.7 ± 0.1 and phase 2: 2.5 ± 0.1) levels were normal for age. GHR (2.2 ± 0.48 ng/ml) levels are higher ($P=0.1$) than GHP (1.17 ± 0.57 ng/ml). Concordance between GHP <2.5 ng/ml and normal IGF1 was demonstrated in 85.3% of patients while between GHR <1 ng/ml and normal IGF1 just in 29.4% ($P<0.01$). Our study shows that in acromegalic patients responsive to SSA, GHP <2.5 ng/ml better than GHR <1 correlate with normal IGF1 levels, thus indicating that evaluation by GHP would more reliably reflect an appropriate disease control.

DOI: 10.1530/endoabs.37.GP.19.06

GP.19.07

Patient experience of living with acromegaly in the UK

Antonia Brooke[1,4], Jacqui Lyttle[3], Lynne Goss[1,4], Louis Pobereskin[2] & South West Peninsula Endocrinology Network[4]
[1]Royal Devon and Exeter NHS Foundation Trust, Exeter, UK; [2]Plymouth Hospitals NHS Trust, Plymouth, UK; [3]JSL Consulting and Associates Ltd, Devon, UK; [4]South West Peninsula Endocrinology Network, Devon and Cornwall, UK.

61 patients (104 invited participants), within 10 years of active treatment for acromegaly, from five hospitals in the South West Peninsula (UK) (one neurosurgical centre) were interviewed to explore the experience of living with acromegaly, access to information, support and their ability to make decisions about their care. Semi-structured interviews by an independent consultant (60–120 min each) included 34 males and 27 females; 25–85 years old; 52 (85%) patients had surgery. 56 (92%) experienced a significant delay from symptoms to diagnosis, but prompt effective secondary care treatment. Communication and coordination of care between teams was criticised. Patients felt a lack of psychological and emotional support. Those in contact with a 'specialist' consultant or an endocrine nurse specialist felt most supported. 52 (85%) felt they had access to a consultant who understood the condition. Those without contact with an endocrine nurse specialist felt their care might have been compromised as a result. Patients felt unprepared for the life-long effect of their condition. 36 (59%) were on additional medical treatment and had issues with the ordering, dispensing or administering of the drug. 46 (75%) would be willing to travel anywhere in the UK to receive treatment (25% to next available hospital) if not available locally. Although, many felt involved in decision-making, few had been offered choice (but would value their consultant's advice). Whilst 53 (87%) patients felt they understood about their condition now, many felt this took a long time with extensive personal research. 67% had been offered written information, 69% had looked on websites, 61% were aware of patient groups but only 20% had joined or sourced information from 1 and 15% attended a meeting (despite a desire to help others with acromegaly). This is the largest acromegaly qualitative patient experience study undertaken in the UK, reflecting the issues of living with acromegaly.

Disclosure
This work has been supported by Ipsen.

DOI: 10.1530/endoabs.37.GP.19.07

GP.19.08

Effects of long-term combined treatment with somatostatin analogues and pegvisomant on cardiac structure and performance in acromegaly

Renata S Auriemma, Ludovica F S Grasso, Mariano Galdiero, Claudia Pivonello, Ciro Salzano, Mariarosaria Negri, Cristina de Angelis, Annamaria Colao & Rosario Pivonello
Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, University 'Federico II', Naples, Italy.

Somatostatin analogues (SA) are known to revert acromegalic cardiomyopathy mainly in young patients with short disease duration, whereas pegvisomant (PEG) reportedly improves cardiac structure and performance in patients resistant to SA. To date, no data are available on the effects of long-term SA+PEG on cardiovascular complications. The current study aimed at investigating the effects of long-term SA+PEG on cardiac structure and performance in acromegaly. Thirty-six acromegalic patients (14M, 22F, aged 52.3 ± 10.2 years) entered the study. Weight, BMI, systolic (SBP) and diastolic (DBP) blood pressure, IGF1, fasting glucose (FG), fasting insulin (FI), HOMA-IR, HbA1c and lipids were evaluated at diagnosis (T0), after long-term (median 36 months, range 6–156 months) SA (T1), and after 12 (T12) and 60 (T60) months of SA+PEG, with last follow up (LFU) being performed after a median time of 78 months (range 60–144 months). At each time point all patients underwent echocardiography. SA induced a slight but not significant decrease in IGF1 ($P=0.077$), whereas FI ($P=0.004$), HOMA-IR ($P=0.013$), ejection fraction (EF, $P=0.013$), early (E) to late (A) ventricular filling velocities (E/A, $P=0.001$) and isovolumetric relaxation time (IVRT, $P=0.000$) significantly improved. At T12 weight ($P=0.004$), BMI ($P=0.005$), IGF1 ($P=0.000$), FI ($P=0.001$), HOMA-IR ($P=0.000$), left ventricular mass index (LVMi, $P=0.000$) and E/A ($P=0.006$) significantly improved compared to T0, with HOMA-IR further improving ($P=0.000$) compared to T1. At T60, IGF1 ($P=0.000$), FI ($P=0.001$), HOMA-IR ($P=0.000$), E/A ($P=0.05$) and IVRT ($P=0.014$) significantly ameliorated compared to T0. At LFU IGF1 normalized in 83.3%; IGF1 ($P=0.000$), FG ($P=0.043$), FI ($P=0.000$), HOMA-IR ($P=0.000$), HDL ($P=0.031$), EF ($P=0.035$), LVMi ($P=0.000$), E/A ($P=0.02$) and IVRT ($P=0.001$) significantly improved compared to T0. PEG dose significantly correlated with LVMi at T12 ($r=0.575$, $P=0.000$) and T60 ($r=0.403$, $P=0.037$). In conclusion, long-term PEG addition to SA improves cardiac structure and performance, particularly diastolic dysfunction, in acromegalic patients resistant to SA.

DOI: 10.1530/endoabs.37.GP.19.08

GP.19.09

Management of pasireotide-induced hyperglycaemia with proactive monitoring and early intervention: key learnings from the phase III, 24-week PAOLA study

Monica R Gadelha[1], Thierry Brue[2], Maria Fleseriu[3], Ilan Shimon[4], Karina Hermosillo Reséndiz[5], Albert Kandra[6], Alberto M Pedroncelli[6] & AnnaMaria Colao[7]
[1]Division of Endocrinology, Medical School and Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil; [2]Hôpital de la Timone, Aix-Marseille University, Centre National de la Recherche Scientifique, and Assistance Publique-Hôpitaux de Marseille, Marseille, France; [3]Northwest Pituitary Center, Oregon Health & Science University, Portland, Oregon, USA; [4]Rabin Medical Center, and Sackler School of Medicine, Tel-Aviv University, Petah-Tiqva, Israel; [5]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; [6]Novartis Pharma AG, Basel, Switzerland; [7]Dipartimento di Medicina Clinica e Chirurgia, Università Federico II di Napoli, Naples, Italy.

Introduction
In PAOLA study, pasireotide showed superior efficacy over continued treatment with octreotide/lanreotide in patients with inadequately-controlled acromegaly; 64% of patients receiving pasireotide long-acting release (LAR) reported hyperglycaemia-related adverse events. Pasireotide has been shown to inhibit insulin secretion. The aim of this exploratory analysis was to investigate the effect of timing of antidiabetic medication (ADM) intervention on the fasting plasma glucose (FPG) outcome during pasireotide LAR treatment.
Methods
Patients randomised to pasireotide LAR, who received ≥ 1 dose of pasireotide and had a valid post-baseline safety assessment (safety population for pasireotide; $n=125$), were included and categorised by baseline diabetic status: non-diabetic; pre-diabetic (FPG 100–<126 mg/dl or HbA1c 5.7–$<6.5\%$ or 2 h post-OGTT glucose 140–<200 mg/dl); diabetic (current/prior ADM use or FPG ≥ 126 mg/dl or HbA1c $\geq 6.5\%$ or 2 h post-OGTT glucose ≥ 200 mg/dl).

Results
Hyperglycaemia (first occurrence of FPG $\geq$126 mg/dl or HbA1c $\geq$6.5% in non-diabetic/pre-diabetic; or first occurrence of FPG or HbA1c increase $\geq$20% from baseline in diabetic) was experienced by 5/19 non-diabetic, 9/24 pre-diabetic and 68/82 diabetic patients. Due to fewer non-diabetic/pre-diabetic patients, the analysis is focused on 68 diabetic patients. ADM was initiated/adjusted in 36/68 diabetic patients after 0–<15 ($n=7$), 15–<30 ($n=8$) or $\geq$30 ($n=21$) days; mean FPG change $\pm$S.D. at week 20 (maximum follow-up) was –110.0$\pm$96.3 mg/dl (from 255.9$\pm$89.8 mg/dl during occurrence of hyperglycaemia), –7.3$\pm$91.1 (from 186.9$\pm$92.2) and 2.1$\pm$78.9 (from 178.7$\pm$38.0), respectively. Mean FPG change was –10.7$\pm$91.5 mg/dl (from 152.4$\pm$44.0) in patients who did not receive ADM ($n=32$). Significant ($P<0.01$) factors predicting hyperglycaemia were BMI $\geq$25 kg/m^2 (OR=2.3), per unit increase in HbA1c (OR=4.3) and diabetes at baseline (OR=4.8); and history of dyslipidaemia (OR=3.6).
Conclusions
Pasireotide-induced hyperglycaemia can be managed with proactive monitoring and early intervention (e.g., within 2 week if FPG >250 mg/dl). These data suggest that in patients receiving pasireotide, early intervention can improve hyperglycaemia control.
Disclosure
This work was supported by Novartis.
DOI: 10.1530/endoabs.37.GP.19.09

GP.19.10

A phase 2 study of antisense oligonucleotide therapy directed at the GH receptor demonstrates lowering of serum IGF1 in patients with acromegaly.

Peter Trainer[1], John Newell-Price[2], John Ayuk[3], Simon Aylwin[4], Aled Rees[5], Will Drake[6], Philippe Chanson[7], Thierry Brue[8], Susan Webb[9], Carmen Fajardo[10], Javier Aller[11], Ann McCormack[12], David Torpy[13], George Tachas[14], Lynne Atley[14] & Martin Bidlingmaier[15]
[1]The Christie NHS Foundation Trust, Manchester, UK; [2]University of Sheffield, Sheffield, UK; [3]University Hospital Birmingham, Birmingham, UK; [4]King's College Hospital, London, UK; [5]Cardiff University, Cardiff, UK; [6]St Bartholomew's Hospital, London, UK; [7]University Paris-Sud, Paris, France; [8]Hopital de la Conception, Marseille, France; [9]Hospital de Sant Pau, Barcelona, Spain; [10]Hospital Universitario La Ribera, Valencia, Spain; [11]Hospital Universitario Puerta de Hierro, Madrid, Spain; [12]St. Vincent Hospital, Sydney, Australia; [13]Royal Adelaide Hospital, Adelaide, Australia; [14]Antisense Therapeutics, Melbourne, Australia; [15]Ludwig-Maximilians University, Munich, Germany.

ATL1103 is a second generation antisense oligomer directed at the GH receptor. It is a 20mer with a phosphorothioate backbone and 2′-*O*-methoxyethyl modifications of the five nucleotides at either end intended to increase its plasma half-life and affinity for the target RNA to allow post-hybridization RNaseH degradation. We report a phase 2 randomised, open-label, parallel group study of subcutaneously administered ATL1103 in patients with active acromegaly. Appropriate ethical approval was obtained in each centre and the study is registered as EudraCT 01200314730. Patients gave written informed consent. The protocol entailed appropriate washout from ongoing medical therapy after which IGF1 had to be at least >1.3 times age-related ULN. Patients were randomised to receive either ATL1103 200 mg once or twice weekly for 13 weeks. After completion of drug administration, patients were monitored for a further 8 weeks. The primary objectives were to evaluate the safety and pharmacokinetics. 34 patients were recruited in 13 centres and 26 (mean age 50.4 years; 11 male) were randomised, and all completed treatment. ATL1103 was well tolerated with mild to moderate injection site reactions being the most common drug-related AE. Four SAEs were reported (three in a single patient) but none were felt to be study drug related. Two patients withdrew at completion of dosing. There was a significant fall in serum IGF1 of 26% by week 14 with 200 mg twice weekly (577$\pm$198 vs 411$\pm$174 ng/ml (mean$\pm$S.D.), $P<0.0001$) although the nadir had not been reached. Once weekly dosing did not result in a significant fall in IGF1. The fall in IGF1 with twice weekly dosing was associated with a mean reduction ring size circumference of 1.150 mm ($P=0.014$) and an increase in GH ($P=0.001$). This study provides proof-of-concept that ATL1103 is able to significantly lower IGF1 in patients with acromegaly.
DOI: 10.1530/endoabs.37.GP.19.10

Pituitary - Hypopituitarism

GP.20.01

Reduced mortality due to malignant neoplasms in patients receiving long-term GH replacement therapy – a Swedish study based on more than 4000 patient-years

Daniel S Olsson[1], Anna G Nilsson[1], Penelope Trimpou[1], Bengt-Åke Bengtsson[1], Eva Andersson[2] & Gudmundur Johannsson[1]
[1]Department of Endocrinology at Sahlgrenska University Hospital, Göteborg, Sweden; [2]Department of Occupational and Environmental Medicine at Sahlgrenska University Hospital, Göteborg, Sweden.

Patients with hypopituitarism and untreated growth hormone (GH) deficiency have excess mortality. GH replacement therapy (GHRT) has many beneficial effects, but its impact on mortality has not been proven and there are still safety concerns regarding the potential cancer risk. We have therefore studied the mortality in non-functioning pituitary adenoma (NFPA) patients with and without GHRT. Only patients with NFPA were studied in order to eliminate the influence of the aetiology of hypopituitarism.
NFPA patients within the Sahlgrenska University Hospital's catchment-area (1.5 million inhabitants) were identified through the Swedish National Patient Registry. The records of all identified patients were reviewed. All patients were cross-referenced with the Swedish National Death Registry. The study period was 1987–2011. Standardised mortality ratios (SMRs) with 95% CIs (reference: Swedish population) were calculated.
We identified 435 patients with NFPA, out of which 433 had complete records and were included in the study. GHRT had been used for at least one year by 187 patients and 246 patients had not been treated with GHRT. Mean ($\pm$S.D.) age at diagnosis was lower ($P<0.001$) in the GHRT-group (54.3$\pm$11.7) than in the non-GHRT-group (64.0$\pm$15.4). Mean duration of GHRT was 10.9 (6.1) years and mean follow-up time in the non-GHRT-group was 6.9 (5.4) years. The total number of deaths in the study was 83. The overall SMR was 0.49 (0.27–0.80, $P=0.003$) for the GHRT-group and 0.98 (0.76–1.24; $P=0.94$) for the non-GHRT-group. The SMR was significantly lower in the GHRT-group compared to the non-GHRT-group ($P=0.02$). SMR for malignant neoplasms was significantly reduced in the GHRT-group (0.19; 0.02–0.68; $P=0.003$), and was not significantly changed in the non-GHRT-group (0.74; 0.37–1.31; $P=0.37$).
This is the first study to report a reduced mortality in NFPA patients receiving long-term GHRT. Furthermore, mortality due to malignant neoplasms was decreased in the GHRT-group and not in the non-GHRT-group.
Disclosure
This study received financial support from the Swedish government under the ALF-agreement.
DOI: 10.1530/endoabs.37.GP.20.01

GP.20.02

Association of serum IGF1 concentration with cardiovascular function in adults with GH deficiency with different GH treatment regimes: a randomised clinical trial

Christa C van Bunderen[1], Rick I Meijer[2], Paul Lips[1], Mark H Kramer[3], Erik H Serné[2] & Madeleine L Drent[1]
[1]Department of Internal Medicine, section Endocrinology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands; [2]Department of Internal Medicine, Institute for Cardiovascular Research (ICaR-VU), VU University Medical Center, Amsterdam, The Netherlands; [3]Department of Internal Medicine, VU University Medical Center, Amsterdam, The Netherlands.

Objective
Epidemiological evidence for a link between serum IGF1 concentration and cardiovascular disease in the general population and in patients with GH deficiency or hypersecretion has been demonstrated. However, the underlying mechanisms remain unresolved. We investigated associations between IGF1 levels within the reference range and different measures of cardiovascular function and risk factors in substituted GH deficient adults within a randomized clinical trial.
Methods
Thirty-two subjects receiving GH therapy for at least a year with a stable IGF1 concentration of -1 to 1 SDS were included and randomised to receive either a decrease of their regular dose (IGF1 target level: -2 to -1 SDS) or an increase of their dose (IGF1 target level: 1 to 2 SDS) for a period of 6 months. Measurements of micro- and macrovascular function, lipid profile, inflammation, and insulin resistance (HOMA-IR) were performed.

Results
Thirty subjects (65.6% male, mean age 46.6 (9.9 s.d.) years) could be analysed. A relationship with vasomotion of skin microvasculatory blood flow measured by skin laser Doppler flowmetry seemed evident. Decreasing GH dose led to a decrease in energy contribution from the local endothelial activity (Δ -0.27 (0.42 s.d.), $P=0.03$), which was significantly different from increasing GH dose ($P=0.03$). There was a trend for a difference between de- and increasing GH dose in the augmentation index during pulse wave analysis in favour of a high-normal IGF1 level ($P=0.06$). Decreasing the GH dose led to an increase in hs-CRP (Δ 1.49 mg/l (3.84 s.d.), $P=0.03$), which was significantly different from increasing GH dose ($P=0.04$). Increasing the GH dose led to an increase in HOMA-IR (Δ 0.38 (0.52 s.d.), $P=0.01$), which was significantly different from decreasing GH dose ($P=0.01$).
Conclusions
IGF1 level within the reference range in GH treated adults is related to microvascular endothelial activity, inflammation, and metabolic insulin resistance.
Disclosure
C C van Bunderen is supported by an AGIKO grant of The Netherlands Organisation for Health Research and Development (ZonMw) (grant number: 92003591). This work was partly supported by an investigator-initiated grant from Pfizer bv.

DOI: 10.1530/endoabs.37.GP.20.02

GP.20.03

Timing is everything? Postpartum pituitary dysfunction – variability of clinical and radiological presentation

Amit Tirosh[1,2], Hiba Masri Iraqi[1,2], Dania Hirsch[1,2], Eyal Robenshtok[1,2], Uri Yoel[3], Yoel Toledano[2,4], Orit Twito[2,5], Gloria Tsvetov[1,2] & Ilan Shimon[1,2]
[1]Endocrine Institute, Rabin Medical Center, Petah Tiqva, Israel; [2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [3]Endocrine Institute, Soroka Medical Center and Ben Gurion University of the Negev, Beer Sheva, Israel; [4]Endocrinology clinic, Division of maternal Fetal Medicine, Helen Schneider Hospital for Women, Rabin Medical Center, Petah Tiqva, Israel; [5]Endocrine Institute, Meir Medical Center, Kfar Saba, Israel.

Introduction
Two aetiologies are responsible for postpartum hypopituitarism; Sheehan's syndrome which develops following traumatic labour, and lymphocytic hypophysitis. Since management of lymphocytic hypophysitis does not require surgery in most cases, pathology is usually absent, and the clinical presentation, in combination with laboratory and imaging characteristics establish the diagnosis. We aimed to describe the various patterns of presentation, including assisting analyses, among women with probable lymphocytic hypophysitis.
Methods
A retrospective study of women with pituitary dysfunction presented immediately or several months following delivery. Clinical characteristics data, pituitary hormone levels, and imaging findings were collected.
Results
Eight women were included; mean age at delivery was 34.8 ± 7.4 years.
Most patients (6/8) presented with breastfeeding difficulty, and 5/8 reported headache. Among the patients with headache, 2/5 presented during pregnancy, and the others – 2, 4 and 9 months following delivery. Hypopituitarism symptoms appeared immediately after delivery in half of the patients, between 7–12 months in 3/8; in one patient severe headache was the sole complaint. All patients had central hypocortisolism, hypogonadotrophic hypogonadism, and growth hormone deficiency, and 7/8 had central hypothyroidism. Prolactin levels were low in 2/8. None of the patients had diabetes insipidus. Five patients passed MRI within 3 months of symptom onset, four of them (80%) complained about headaches. These patients had either normal pituitary structure (2/5), pseudo-adenoma (1/5) or diffusely enlarged and hyperintense gland, suggestive for hypophysitis (2/5). Three patients have been diagnosed more than a year following presentation, all had reduced pituitary volume on MRI, and two of them had panhypopituitarism.
Conclusion
Over 300 cases of autoimmune hypophysitis were reported in the literature. Thus, a high index of suspicion is required to identify women in the postpartum period with breastfeeding difficulty, with or without headaches, and to study their pituitary function.

DOI: 10.1530/endoabs.37.GP.20.03

GP.20.04

Irradiation-induced hypopituitarism in adult brain tumour survivors: single-centre longitudinal data

Nikolaos Kyriakakis[1], Julie Lynch[1], Susan C Short[2], Paul Hatfield[2], Carmel Loughrey[2], Georgina Gerrard[2], Steve M Orme[1] & Robert D Murray[1]
[1]Endocrinology, Leeds Centre for Diabetes and Endocrinology, St James's University Hospital, Leeds, UK; [2]Oncology, Leeds Cancer Centre, St James's University Hospital, Leeds, UK.

Introduction
Radiation-induced hypopituitarism is a well-recognized complication of cranial radiotherapy (cXRT) for childhood brain tumours when the hypothalamo–pituitary axis is within the irradiation field. Few data are available for survivors of adult brain tumours who have received cranial irradiation.
Methods
We retrospectively reviewed medical records of patients referred to Endocrinology following cXRT for primary non-pituitary brain tumours during adulthood. Longitudinal data regarding pituitary-related treatment outcomes were collected. The ITT and/or GST were used to assess GH and HPA axes integrity. Basal values for the additional anterior pituitary hormones were used to determine gonadotropin, TSH and prolactin status.
Results
107 patients (mean age 40.0 ± 13.1 years) with mean duration of post-cXRT follow-up of 9.1 ± 5.7 years were studied. 32.7, 19.6, 20.6 and 27.1% of patients had tumours located in the anterior, middle, posterior cranial fossa and central (perisellar) regions respectively. 94.4% received fractionated photon radiotherapy (mean dose 51.7 ± 6.5Gy, mean number of fractions 28.6 ± 3.5), while the remaining patients received proton beam or stereotactic radiotherapy. Evidence of pituitary dysfunction was present in 88.8% of patients. The GH axis was affected in 86.9% of patients (severe GHD 64.5%, partial GHD 22.4%), followed by LH/FSH (34.6%), ACTH (23.4%), and TSH (11.2%) axes. Clinically significant ACTH deficiency necessitating glucocorticoid replacement was present in only 10.3% of cases. Hyperprolactinaemia was noted in 15.0% of patients. Single pituitary axis dysfunction was found in 41.1% of patients, while multiple axes were affected in 47.7% of cases. Longitudinal data analysis showed accumulation of pituitary hormone deficits the longer the duration of follow-up.
Conclusions
Pituitary dysfunction in survivors of adult brain tumours following cXRT is very common. The majority of deficits develop within 5 years post-cXRT, however late onset or progression of severity of a previously developed hormone deficiency was also observed. Long-term follow-up of these patients in specialist endocrine centres is strongly recommended.

DOI: 10.1530/endoabs.37.GP.20.04

GP.20.05

Long-term follow-up of 520 patients with non-functioning pituitary adenomas from two large tertiary referral centres: a UK-Republic of Ireland collaborative study

Michael O'Reilly[1], Saket Gupta[2], C A Thompson[2], Harriet Pearce[1], Gabriella Bugg[1], Andrew Toogood[1], Neil Gittoes[1], Christopher Thompson[2] & John Ayuk[1]
[1]University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; [2]Beaumont Hospital, Dublin, Ireland.

Abstract
Non-functioning pituitary adenomas (NFPAs) are the most common pituitary tumours, often presenting with chiasmal compression or hypopituitarism. Surgical resection, accompanied by radiotherapy (RTX) in selected cases, is the treatment of choice for compressive tumours. Long-term health consequences of NFPAs and their treatment are unclear. In this retrospective study, we aimed to assess long-term pituitary function, recurrence and mortality in a large NFPA cohort across two tertiary centres. Case-note review of all patients treated for NFPA in Queen Elizabeth Hospital Birmingham and Beaumont Hospital Dublin between 1997 and 2012 was performed; data on patients treated before 1997 was included where available. Clinical presentation, imaging characteristics, long-term pituitary function and co-morbidities were recorded in each case. Data on mortality was recorded via Clinical Portal in Birmingham and from GP contact in Dublin.
519 patients were included in the analysis (Birmingham $n=271$; Beaumont $n=248$; 59.2% male, mean age at presentation 55.2 ± 14.1 years). Mean duration of follow-up was 8.5 ± 6.3 years (0.5–43). 90.8% of patients underwent surgery (81.1% transsphenoidal). 184 patients (35.4%) underwent pituitary radiotherapy, either postoperatively (43.5%) or at recurrence

(56.5%). Tumour regrowth was recorded in 35.6% of cases; mean time to regrowth was 47.6±51.6 months, (range 1–276). The incidence of panhypopituitarism was higher in irradiated patients (49.4% vs 38.1%, $P<0.001$). The incidence of second intracranial tumours was 3.2% and 0.6% in irradiated and non-irradiated patients respectively, $P<0.001$. 75 patients (14.5%) died during follow-up. Mean age at death in RTX and RTX-naïve patients was 69.8±12.7 vs 77.7±9.8 years, respectively, $P=0.006$.

This large collaborative study between Britain and Ireland highlights important health consequences in patients treated for NFPA. Tumour recurrence may occur many years after initial treatment, necessitating lifelong follow-up. Pituitary irradiation may have consequences on the risk of secondary intracranial tumours and on mortality. Further analysis is required to understand the associations observed here.

DOI: 10.1530/endoabs.37.GP.20.05

GP.20.06

Somatic complaints, pain and health related quality of life in patients treated for secondary adrenal insufficiency – results from a randomised controlled trial

Jorien Werumeus Buning[1], Pauline Brummelman[1], Janneke Koerts[2], Robin P F Dullaart[1], Gerrit van den Berg[1], Melanie M van der Klauw[1], Oliver Tucha[2], Bruce H R Wolffenbuttel[1] & André P van Beek[1]
[1]University Medical Center Groningen, Groningen, The Netherlands; [2]University of Groningen, Groningen, The Netherlands.

Introduction

There is growing evidence that quality of life (QoL) in patients with adrenal insufficiency (AI) is impaired. Undertreatment with glucocorticoids is associated with symptoms such as fatigue and gastrointestinal complaints whereas overtreatment is associated with impaired QoL. However, evidence for this is derived from observational studies which are prone to bias. Therefore, the aim of the present study was to compare two different physiological doses of hydrocortisone (HC) on somatic complaints, pain and QoL in an RCT.

Methods

Forty-seven patients (29 males, 18 females; mean (S.D.) age, 51(14) years) with secondary AI participated. In this RCT with cross-over design, patients received first a lower dose of HC (0.2–0.3 mg/kg body weight/day in three divided doses) for 10 weeks followed by a higher dose of HC (0.4–0.6 mg/kg body weight/day in three divided doses) for 10 weeks, or vice versa. Health related quality of life was assessed with questionnaires after each treatment period and daily with a mood and symptom checklist.

Results

After 10 weeks on the higher dose of HC patients reported significantly fewer depressive symptoms ($P=0.016$) (Hospital Anxiety and Depression Scale), less general and mental fatigue ($P=0.004$ and $P=0.003$, respectively), less reduced motivation ($P=0.021$) (Multidimensional Fatigue Inventory-20) compared to the lower dose. Furthermore, after treatment with the higher dose patients reported better physical functioning ($P=0.041$), general health ($P=0.013$) and more vitality ($P=0.025$) (RAND-36). In addition, while on the higher dose fewer somatic symptoms ($P=0.022$) (Patient Health Questionnaire-15) and less pain ($P < 0.001$) were experienced.

Conclusion

While on the higher dose of HC, patients reported a better quality of life with regard to general health, mental health, depressive symptoms, common somatic complaints, pain and fatigue compared to the lower dose of HC.

DOI: 10.1530/endoabs.37.GP.20.06

GP.20.07

Outcome and prognosis of typical and atypical pituitary adenomas in a monocentric experience

Sabrina Chiloiro[1], Francesco Doglietto[2], Donato Iacovazzo[1], Antonella Giampietro[1], Francesco Di Nardo[3], Chiara de Waure[3], Libero Lauriola[4], Annunziato Mangiola[5], Carmelo Anile[5], Giulio Maira[5], Laura De Marinis[1] & Antonio Bianchi[1]
[1]Section of Endocrinology, Department of Internal Medicine, Catholic University, School of Medicine, Rome, Italy; [2]Neurosurgery, University of Brescia, Brescia, Italy; [3]Institute of Hygiene, Catholic University, School of Medicine, Rome, Italy; [4]Institute of Anatomic Pathology, Catholic University, School of Medicine, Rome, Italy; [5]Institute of Neurosurgery, Catholic University, School of Medicine, Rome, Italy.

Background and objective

Atypical pituitary adenomas (APA), in 2004, were defined according to WHO classification, as those with Ki-67>3%, excessive p53 expression and increased mitotic activity and invasive behaviour. The real usefulness of this classification is still controversial, so we reviewed compared clinical and prognostic features in our typical and atypical pituitary adenomas.

Patients and methods

We retrospectively reviewed 343 consecutive pituitary adenomas (PAs). APAs occurred in 18.7% of cases. All patients were operated on in the Department of Neurosurgery at our institution and followed up at the Hypothalamic-Pituitary Disease Unit of the same institution. None patient had an adjuvant treatment pre-neurosurgery. Median follow-up time in our series was 75 months (range: 7–345 months).

Results

More frequently APAs were diagnosed in younger patient. However we found a similar prevalence of APAs in male and female patients. A higher risk of being affect for an APA was identified in cases characterised by an ACTH- and PRL-immunohistochemical positivity. According to WHO classification, cavernous sinus invasion was associated with higher risk of being affected of an APA and consequently a higher risk of a partial PA neurosurgery resection. In our series we separately analysed recurrence and disease free survival time (DFST) in patients undergone radical neurosurgery (219 cases). In this group of radically resected PAs, we find a similar risk of recurrence-disease and a superimposable DFST between typical and atypical pituitary adenomas. Moreover, in this series we found that Ki-67 expression>1.5% was associated to a higher risk of recurrence and to a worse DFST, even after correction for age at diagnosis, gender, immunohystochemical classification, tumor size, invasiveness and Knosp classification ($P=0.01$; HR: 2.572; 95% CI: 1.251–5.285). PAs with Ki-67>1.5% showed a worse DFST as compared to PAs with Ki-67<1.5% (HR: 2.166; 95% CI: 1.154–4.064).

Conclusion

In this series, atypical and typical PAs didn't differ for recurrence and DFST. PAs with Ki-67≥1.5% showed a higher recurrence risk and a worse DFST as compared to PAs with Ki-67<1.5%. We suggest that a Ki-67≥1.5% may be useful as prognostic marker.

DOI: 10.1530/endoabs.37.GP.20.07

GP.20.08

'Pseudo-resistance' in macroprolactinomas treated with dopamine agonists; recognising delayed radiological response and a role for ^{11}C-methionine PET-CT in guiding management

Andrew S Powlson[1], Olympia Koulouri[1], Andrea Steuwe[2], Daniel Gillett[2], Sarah Heard[2], Andrew Hoole[3], Miriam Scott[1], Benjamin G Challis[1], Nagui Antoun[4], Heok K Cheow[4], Richard J Mannion[5] & Mark Gurnell[1]
[1]Metabolic Research Laboratories, Institute of Metabolic Science, University of Cambridge, Cambridge, UK; [2]Department of Nuclear Medicine, Addenbrooke's Hospital, Cambridge, UK; [3]Department of Medical Physics, Addenbrooke's Hospital, Cambridge, UK; [4]Department of Radiology, Addenbrooke's Hospital, Cambridge, UK; [5]Department of Neurosurgery, Addenbrooke's Hospital, Cambridge, UK.

Background

Endocrine Society guidelines classify macroprolactinomas as 'resistant' if there is failure to normalise prolactin, or to achieve radiological tumour shrinkage of >50%, on standard doses of dopamine agonist. In this context, escalation of treatment to maximal tolerable doses and/or referral for surgery is advised. However, we have recently observed several 'discordant responders', where tumour shrinkage lags significantly (>6 months) behind the biochemical response, but is ultimately achieved without treatment escalation.

Methods

i) A Pubmed search for 'medical treatment of prolactinomas' was performed & papers reporting discordance between biochemical and radiological responses identified and ii) We searched our pituitary database for patients treated locally over a 10-year period. A case where ^{11}C-methionine PET-CT was used to guide management is described.

Results

From an initial return of 845 papers, 21 provided sufficient information, describing 340 patients, 92 of whom exhibited a discordant response. Of 89 macroprolactinomas in our local database, we identified 14 patients in whom prolactin normalised, but tumour shrinkage was <50% at >6 months after commencing treatment. One of these, a 36-year-old man (initial prolactin 14,123mU/l) achieved biochemical normalisation within eight weeks; however, despite continued prolactin suppression (28mU/l; 500mcg twice-weekly) at 12 months his tumour showed no reduction in size. Reassuringly, ^{11}C-methionine PET-CT coregistered with MRI demonstrated a complete absence of tracer uptake in the 'residual adenoma'. With this evidence, contrary to Endocrine Society

Guidelines, cabergoline was reduced to 250mcg twice-weekly. 24-months later serum prolactin remained well-controlled (76 mU/l), and substantial (>50%) tumour shrinkage was evident on MRI.
Conclusions
These cases demonstrate that a delayed radiological response may be seen without further dose escalation, once biochemical normalisation has been achieved in prolactinomas; current guidelines may therefore inappropriately categorise such tumours as 'dopamine agonist resistant'. Our literature and local database review suggests this may be an under-recognised phenomenon. Furthermore, the case described here highlights the utility of functional imaging in aiding management in such patients.

DOI: 10.1530/endoabs.37.GP.20.08

GP.20.09

Thyrotropinoma: diagnosis and management of a rare but increasingly recognised pituitary tumour – novel insights from a large prospective UK study

Olympia Koulouri[1,2], Carla Moran[2], Andrew Powlson[1,2], Nagui Antoun[2], Neil Donnelly[2], Richard Mannion[2], John Pickrd[1,2], David Halsall[1,2], Krish Chatterjee[1,2] & Mark Gurnell[1,2]
[1]University of Cambridge, Cambridge, UK; [2]Addenbrooke's hospital, Cambridge, UK.

Background
Thyrotropinomas (TSHomas) are traditionally considered a rare, albeit important cause of thyrotoxicosis. Although early case series reported a predominance of invasive macroadenomas, emerging evidence suggests microadenomas are being increasingly diagnosed, and the clinical/biochemical phenotype appears to be more variable than previously suspected. We therefore performed detailed phenotyping of patients referred to our centre with a diagnosis of TSHoma over a 4-year period.
Methods
35 patients with hyperthyroxinaemia and non-suppressed TSH were studied prospectively. Laboratory assay artefact, confounding intercurrent illness/drug therapy and *THRB* mutations were excluded in all cases. Further investigations included: hyperthyroid symptom score, measurement of resting energy expenditure, sleeping heart rate, bone mineral density, sex hormone-binding globulin (SHBG), alpha-subunit (ASU):TSH molar ratio, TRH test, OGTT, octreotide (100 mcg) suppression test (OST), volumetric MRI (vMRI) and ^{11}C-methionine PET-CT. Patients then proceeded to a formal trial of depot somatostatin analogue (SSA) therapy.
Results
Clinical/metabolic features varied markedly, ranging from euthyroid to overtly hyperthyroid, and were not clearly correlated with the degree of hyperthyroxinaemia. Similarly, SHBG and ASU:TSH did not reliably identify many cases (both raised in <50%), especially microadenomas. In contrast, a blunted TSH response to TRH (<4.5-fold rise), combined with normalization of thyroid function during a 3 month trial of SSA therapy, was observed in 90% of cases. Interestingly, TSH and FT3 responses in the OST did not predict efficacy of depot SSA. 50% of patients had microadenomas, with several not reliably visualised using conventional MRI. In these patients, vMRI combined with PET/CT identified the site of the microadenoma. All 35 patients received SSA as a bridge to surgery or as long-term treatment where pituitary surgery was deemed inappropriate.
Conclusions
Modern diagnostic algorithms for TSHomas should place greater emphasis on the TRH test and response to depot SSA therapy. vMRI and functional imaging may aid visualisation/confirm the site of a suspected microadenoma and thereby guide surgical resection.

DOI: 10.1530/endoabs.37.GP.20.09

Pituitary - Diagnosis of Cushing's disease

GP.21.01

A reappraisal of second line tests in the differential diagnosis of ACTH-dependent Cushing's syndrome: the role of three dynamic tests

Mattia Barbot[1], Laura Trementino[2], Filippo Ceccato[1], Marialuisa Zilio[1], Nora Albiger[1], Marco Boscaro[1], Giorgio Arnaldi[2] & Carla Scaroni[1]
[1]Endocrinology Unit, Department of Medicine DIMED, University Hospital, Padova, Italy; [2]Endocrinology Unit, Università Politectnica delle Marche, Ancona, Italy.

Introduction
The diagnosis of Cushing's syndrome (CS) might be challenging especially in ACTH-dependent CS when it comes to detect the origin of ACTH secretion.
Materials and methods
We retrospectively recorded data about 170 patients with ACTH-dependent CS (149 CD, 21 EAS) referring to two Endocrinology Units. We focused especially on the performance of 3 dynamic tests: the dexamethasone 8 mg overnight challenging (HDDST), the CRH and the desmopressin (DDAVP) test.
Results
Patients with EAS were slightly older and had higher 0800 h. ACTH levels, 0800 h. and after 1 mg dexamethasone cortisol levels, and UFC than patients with CD ($P<0.01$). On the contrary CD patients had a greater ACTH and cortisol response after CRH injection ($P<0.0001$) and also a more pronounced decreased of cortisol after HDDST ($P<0.0001$). A threshold for ACTH increase after CRH stimulation of 72% was able to identify CD with a sensitivity (SE) of 93% (95% CI: 68–83%) and a specificity (SP) of 82% (95% CI: 83–100%). Regarding HDDST, a cortisol reduction >53% suggested a pituitary origin with SE of 88% (95% CI: 81–93%) and SP of 90% (95% CI: 68–99%); the latter could be increased to 100% by moving the cut-off to 75% of decrease. The AUC of CRH test and HDDST was 0.93 (95% CI: 0.89–0.97) in both cases (P=ns). There were no EAS with both positive responses to these 2 tests. ACTH and cortisol increases after DDAVP test were also higher in CD than in EAS ($P<0.01$), but they added very little to the power of the other dynamic tests.
Conclusions
Patients with CD showed an increased response to both HDSST and CRH; the cut-offs found had good SE and SP in discriminating patients with CD from those with EAS. Lack of response of both tests was highly suggesting of EAS. On the contrary when both tests gave positive responses it indicated CD. We also confirmed the limited role of DDAVP test in this diagnostic phase. In conclusion, dynamic tests may play an important tool in the differential diagnosis of ACTH-dependent CS.

DOI: 10.1530/endoabs.37.GP.21.01

GP.21.02

Bilateral inferior petrosal sinus sampling reliably differentiates pituitary from ectopic Cushing's, but frequently fails to predict pituitary tumour location, especially when lateralizing to the right

Olympia Koulouri[1,2], Nishita Nigam[1], Andrew Powlson[1,2], Neil Donnelly[2], Richard Mannion[2], John Pickard[1,2], Brendan Koo[2], David Halsall[1,2] & Mark Gurnell[1,2]
[1]University of Cambridge, Cambridge, UK; [2]Addenbrooke's hospital, Cambridge, UK.

Background
BIPSS remains the gold standard for differentiating pituitary and ectopic sources in ACTH-dependent Cushing's syndrome. A pituitary:peripheral ACTH ratio >2 in the basal state, and/or >3 following CRH stimulation, is considered indicative of pituitary Cushing's, with a range of sensitivities and specificities cited in the literature. In addition, in Cushing's disease a peak interpetrosal gradient of >1.4 has been reported to predict the site of the adenoma in approximately 2/3 of cases. We examined the performance of BIPSS against these criteria in a cohort of patients who had undergone the procedure in our centre over the last decade.
Methods
39 patients with biochemically proven ACTH-dependent Cushing's, who had undergone BIPSS and had either subsequent histological confirmation of the ACTH source, or significant improvement/cure of their Cushing's following transsphenoidal surgery, were included in the study.
Results
Based on basal ACTH levels (pre-CRH stimulation), 89% of patients were deemed to have pituitary Cushing's and 11% an ectopic source. Post-CRH stimulation 94% of patients reached the cut-off for pituitary Cushing's. This gave a sensitivity of 97% and a specificity of 100% for pre-CRH stimulation and 100% sensitivity and 67% specificity for post-CRH stimulation. Two thirds (65%) of BIPSS procedures exhibited lateralisation to the right side, but this was subsequently shown at surgery to be correct in only half of the patients. In contrast, left lateralisation had a much higher positive predictive value (80%). When combined, lateralisation (either right or left) was accurate in only 60% of cases.
Conclusions
Predominance of right sided lateralisation on BIPSS may signify a 'dominant' right sinus in many patients undergoing this procedure. We suggest therefore that whole gland exploration is particularly important in 'right sided' BIPSS cases, and additional pituitary imaging (e.g. volumetric MRI, functional imaging) may be helpful in informing the surgical approach.

DOI: 10.1530/endoabs.37.GP.21.02

GP.21.03

Altered neural processing during emotional faces in remitted Cushing's disease

Cornelie Andela[1,3], Janna Marie Hoogendam[1,3], Steven Van der Werff[1,3], Nienke Pannekoek[1,3], Henk Van Steenbergen[2,3], Onno Meijer[1,3], Mark Van Buchem[1,3], Serge Rombouts[1,3], Roos Van der Mast[1], Nienke Biermasz[1,3], Nic Van der Wee[1,3] & Alberto Pereira[1,3]

[1]Leiden University Medical Center, Leiden, The Netherlands; [2]Institute of Psychology Leiden University, Leiden, The Netherlands; [3]Leiden Institute of Brain and Cognition, Leiden, The Netherlands.

Background

Patients with long-term remission of Cushing's disease (CD) demonstrate residual psychological complaints. At present, it is not known how previous exposure to hypercortisolism affects psychological functioning in the long-term. In foregoing Magnetic Resonance Imaging (MRI) studies, abnormalities of brain structure and resting-state connectivity were demonstrated in patients with long-term remission of CD. However, no data are available on functional alterations in the brain during the performance of emotional or cognitive tasks in these patients.

Objective

To investigate brain activation during emotion processing in patients with long-term remission of CD.

Design

A cross-sectional functional MRI study.

Methods

Processing of emotional faces versus a non-emotional control condition was examined in 21 patients with long-term remission of CD and 21 matched healthy controls. Functional MRI analyses focused on activation and connectivity of two a priori determined regions of interest: the amygdala and the medial prefrontal cortex (mPFC). In addition, we assessed psychological and cognitive functioning, and clinical disease severity.

Results

Patients with long-term remission of CD showed hypoactivation in the mPFC during processing of emotional faces in patients relative to controls. In addition, functional coupling between the mPFC and posterior cingulate cortex (PCC) was decreased. No differences were found in the activation of the amygdala.

Conclusion

The present study is the first to show alterations in brain function and functional coupling in patients with long-term remission of CD relative to matched healthy controls. These alterations in brain function may, together with abnormalities in brain structure, explain the persisting psychological morbidity these patients after long-term remission.

DOI: 10.1530/endoabs.37.GP.21.03

GP.21.04

Exaggerated and additive ACTH responses following the combined ghrelin + CRH test in patients with Cushing's disease

Dragana Miljic[1,2], Snezana Polovina[3], Mirjana Doknic[1,2], Sandra Pekic[1,2], Marko Stojanovic[1], Milan Petakov[1,2], Vera Popovic[1,2] & Dragan Micic[1,2]

[1]Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia, Belgrade, Serbia; [2]Medical Faculty, Belgrade University, Belgrade, Serbia; [3]Obesity Outpatient Clinic, Clinical Center of Serbia, Belgrade, Serbia.

Ghrelin is able to stimulate HPA axis in both humans and animals. Exaggerated ACTH and cortisol responses to ghrelin have been shown in patients with CD. Here we studied the role of ghrelin alone or in combination with CRH in the diagnosis of CD. In 21 CD patient (18 female, age 49.8 ± 10.2 years, BMI 29.8 ± 0.8 kg/m^2, ten macroadenomas 11 microadenomas) we performed: i) ghrelin test (100 μg iv bolus) ii) CRH test (100 μg iv bolus) and iii) ghrelin + CRH, in random order, one week apart. We also included 8 (seven female, age 40.6 ± 5.3 years, BMI 29.9 ± 1.2 kg/m^2) control subjects (C) in the study. Peak ACTH, cortisol, PRL and GH responses to ghrelin and/or CRH were evaluated (mean ± S.E.). At baseline, ACTH (CD: 71.2 ± 15.6 ng/l; C: 18.9 ± 4.1 ng/l; $P < 0.01$) and cortisol levels (CD: 643.1 ± 41.7 nmol/l; C: 316.4 ± 23.7 nmol/l $P < 0.01$) were significantly higher in CD vs C. After ghrelin administration peak ACTH (CD: 192.3 ± 40.4 ng/l vs C: 71 ± 30.9 ng/l, $P < 0.01$) and cortisol responses (CD: 979.8 ± 46.5 nmol/l vs C: 529.3 ± 74.8 $P < 0.01$) were significantly higher in CD compared with C but similar with ACTH (CD: 179 ± 26.5 ng/l vs C: 59.8 ± 12.3 ng/l, $P < 0.01$) and cortisol responses (CD: 1088.7 ± 51.4 nmol/l vs C: 677.3 ± 71.3 nmol/l, $P < 0.01$) to CRH in both patients with CD and controls. Following the co-administration of ghrelin + CRH an additive ACTH response was observed in both groups (CD: 384.1 ± 74.2 ng/l; C: 176.3 ± 48.5 ng/l) but at a different level. ACTH and cortisol responses, during all three tests, were similar in CD patients with micro- and those with macroadenomas. After stimulation with ghrelin the peak PRL responses (CD: 1046.6 ± 179.7 mU/l; C: 998.4 ± 222.4 mIU/l; $P > 0.05$) were similar in CD compared to C, while GH responses (CD: 21.2 ± 3.7 mIU/l; C: 54.6 ± 9.1 mU/l; $P < 0.05$) were significantly lower in CD. Our results show that ACTH and cortisol secretion remain regulated and responsive to trophic stimuli in patients with CD, which are characterised by exaggerated ACTH and cortisol responses to ghrelin and CRH. Additive ACTH responses to the combined ghrelin + CRH administration, suggest that their ACTH releasing activities may be mediated independently in both patients and controls.

Disclosure

This work was supported by the Serbian Ministry of Science Grant project number 175033

DOI: 10.1530/endoabs.37.GP.21.04

GP.21.05

Mental fatigue and executive dysfunction in patients with Cushing's syndrome in remission

Eleni Papakokkinou[1], Peter Berglund[2], Birgitta Johansson[2] & Oskar Ragnarsson[1]

[1]Section for endocrinology, Department of Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden; [2]Department of Clinical Neuroscience and Rehabilitation, Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.

Background

Patients with Cushing's syndrome (CS) in remission often suffer from impaired quality of life and cognitive dysfunction. Mental fatigue is characterized by mental exhaustion which appears especially during sensory stimulation or following mentally strenuous tasks. Other typical features are long recovery time for restoration of mental energy, irritability, impaired memory and concentration and sensitivity to stress, light and noise. The primary aim of this study was to investigate the occurrence of mental fatigue by using the recently developed mental fatigue scale (MFS) in patients with CS in remission. The secondary aim was to examine whether the more demanding parts C and D of the trail making test (TMT) are more sensitive, compared to the conventional parts A and B, to evaluate speed proceeding, visual search, motor performance and executive functioning.

Methods

This was a cross-sectional study including 51 patients with CS in remission and 51 controls, matched by age, gender and education. All subjects completed the self-administrated MFS and performed all four parts of the TMT.

Results

The mean (± S.D.) age of patients and controls was 52.5 ± 14.6 years and 53.6 ± 13.9 years ($P = 0.7$), respectively. The median time in remission was 12 (4–18) years. The patients had higher scores on all components of the MFS, indicating worse outcome, except for sensitivity to noise. The mean total score on the MFS was 13.5 ± 7.4 in the patients compared to 7.8 ± 4.9 ($P < 0.001$) in controls. After adjustment for fatigue, depression and anxiety the patients performed worse on part D of the TMT ($P < 0.05$) but not on parts A, B and C.

Conclusions

Mental fatigue is common in patients with CS in remission. The most demanding part of the TMT, part D, is more useful to capture cognitive deficits in patients with CS in remission compared to the conventional parts A and B.

Disclosure

This project received financial support from the Swedish federal government under the LUA/ALF agreement and The Health and Medical Care Committee of the Regional Executive Board, Region Vastra Gotaland.

DOI: 10.1530/endoabs.37.GP.21.05

GP.21.06

Prolactine and urinary free cortisol measurement improve inferior petrosal sinus sampling results in ACTH dependent Cushing's Syndrome

Carmen Fajardo Montañana[1,2], Lucia Camarena Navarro[1], Ma Dolores Ferrer Puchol[2], Carmen Valldecabres Ortiz[2], Jose Gomez Vela[2] & Pedro Riesgo Suarez[2]
[1]Hospital Universitario de La Ribera, Alzira, Spain; [2]Facultad de Medicina. Universidad Católica San Vicente Martir (UCV), Valencia, Spain.

Introduction
Inferior petrosal sinus sampling (IPSS) is considered to be the gold standard for confirming the source of ACTH secretion in patients with Cushing's syndrome (CS). Prolactin measurement during IPSS can improve diagnostic accuracy and reduces false negative responses.
Patients and methods
56 patients with ACTH-dependent CS were included (45 F/11 M, mean age 43.6 ± 10.8 years and 90.1% Cushing's disease) diagnosed since 2000. IPSS was performed in 27 cases (15 with PRL measurement, two excluded due to incomplete data). Depending on IPSS results were classified as typical IPSS response if basal ACTH ratio Central/peripheral (C/P) was >2 and/or after CRH >3, considering others as atypical. Response to surgical treatment and utility of PRL determination were analyzed.
Results
Cortisol response to high DXM suppression test was $>50\%$ in 62.9%, and $>90\%$ in 37% in Cushing's disease. Preoperative pituitary MRI did not identify adenoma in 12.5%. MRI adenoma lateralization was concordant with surgical adenoma lateralization in 92.7%. IPPS was typical in 46.3% (6/13) and there were significant differences typical vs atypical (basal ACTH C/P ratio, ACTH C/P ratio after CRH, peak time, urinary free cortisol (UFC) and PRL correction). Basal PRL ratio C/P was <1.8 in all atypical IPPS and 50% of typical IPPS. Venograms were reviewed and ACTH C/P peak corrected with PRL was >0.8 in Cushing's disease, being most of them >1.2 (5/7). Only two patients have an intermediate value (a cyclic Cushing's disease 1.09 and a microadenoma 1.05). Four patients with atypical IPPS corrected with PRL were referred to surgery and they meet remission criteria up today. After transsphenoidal surgery 90.9% of patients met remission criteria (100% of microadenomas and in those without previous MRI image).
Conclusion
PRL measurement in atypical IPSS allows reclassification, whereas in typical cases can be useful to validate the peak ACTH C/P. PRL elevation after CRH and its use in the correction of the ACTH C/P ratio does not interfere with the interpretation of ACTH C/P peak. It is essential to evaluate UFC to complete the assessment

DOI: 10.1530/endoabs.37.GP.21.06

Pituitary - Therapy of Cushing's disease

GP.22.01

Phase III, multicentre, double-blind, randomised withdrawal study of osilodrostat (LCI699) in patients with Cushing's disease: a study design

Akira Shimatsu[1], Nicholas Sauter[2], Roxzana Kelly[2], Peter Unge[3], Xin Zhi[2] & Maria Fleseriu[4]
[1]Clinical Research Institute, National Hospital Organization Kyoto Medical Center, Kyoto, Japan; [2]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; [3]Novartis Pharma AG, Basel, Switzerland; [4]Northwest Pituitary Center, Oregon Health & Science University, Portland, Oregon, USA.

Introduction
Osilodrostat is a potent, oral inhibitor of 11β-hydroxylase, the enzyme that catalyses final step of cortisol biosynthesis. In a phase II study, 15/19 patients treated with osilodrostat met the primary endpoint (normal urinary free cortisol (UFC) at 22 weeks); osilodrostat was generally well tolerated. This phase III study aims to confirm the efficacy and long-term safety of osilodrostat.
Patients and methods
Adults (18–75 years) with persistent or recurrent CD post-surgery and/or post-irradiation or with *de novo* CD not considered surgical candidates.
Design
Phase III, multicentre, double-blind, randomised withdrawal study of osilodrostat. Period 1 (week 1–12): Osilodrostat will be initiated at 2mg bid and dose adjusted (range: 1–30 mg bid) based on UFC and patient's safety. Period 2 (week 13–24): Stable dose. Period 3 (wk 26–34): 8-week, double-blind, placebo-controlled randomised withdrawal phase. Patients with mean UFC (mUFC) $\leq$ULN at week 24 and with no dose increase above dose level established at week 12, will be randomised (1:1) at week 26 to continue the same dose of osilodrostat or to receive matching placebo. Patients who are non-responders (UFC $>1.5\times$ULN) will discontinue from randomised withdrawal and resume open-label osilodrostat. Non-randomised patients will continue to receive open-label osilodrostat. Period 4 (week 34–48): Single-arm, open-label osilodrostat treatment for all patients. Endpoints: Primary: proportion of randomised patients in each treatment group with mUFC $\leq$ULN at week 34. Key secondary: proportion of patients with mUFC $\leq$ULN at week 24 with no dose increase above the level established at week 12.
Conclusion
This study design, with a short (8-week) double-blind, placebo-controlled randomised withdrawal period, following a 24-week run-in period of open-label osilodrostat treatment allows assessment of efficacy (versus placebo) and long-term safety of osilodrostat in a larger CD population. This design is well suited to patients with rare and serious diseases such as CD as long-term placebo-controlled studies would be difficult to conduct.
Disclosure
This work was supported by Novartis.
DOI: 10.1530/endoabs.37.GP.22.01

GP.22.02

Surgical outcome and factors associated with Cushing's disease recurrence in 101 consecutive patients operated on by a single pituitary neurosurgeon: the Cleveland Clinic experience

Philip C Johnston[1], Amir H Hamrahian[1], Jim Bena[2], Bob Weil[3] & Laurence Kennedy[1]
[1]Department of Endocrinology, Diabetes and Metabolism, Cleveland Clinic, OH, USA, Cleveland, Ohio, USA; [2]Department of Biostatistics, Quantitative Health Sciences, Cleveland Clinic, OH, USA, Cleveland, Ohio, USA; [3]Department of Neurosurgery, Geisinger Health System, Danville, PA, USA, Pennsylvania, USA.

Background
Transsphenoidal tumour resection (TSS) is the first-line treatment for Cushing's disease (CD). With an experienced neurosurgeon, immediate remission rates $>80\%$ are expected for patients with microadenomas (<10 mm).
Aim
To report initial and long-term remission rates in a specialist centre, and to ascertain factors associated with disease recurrence after TSS.
Methods
Patients with CD ($n=101$, 28M, 73F) having TSS by one neurosurgeon (RJW) at Cleveland Clinic between 2004 and 2013, with a minimum one-year follow-up. Glucocorticoids were withheld during and immediately after surgery; ACTH and cortisol were closely monitored postoperatively with a standard protocol to determine initial remission. After discontinuing hydrocortisone for surgically-induced adrenal insufficiency, long-term recurrence was defined by 24 h UFC $>$ULN, and/or late night salivary cortisol $>$ULN, and/or 8 AM serum cortisol >1.8 mcg/dl after 1 mg overnight dexamethasone.
Results
Median (range) for age and follow up were 46 (15–87) and 4.33 (1–9.8) years, respectively. 74 patients had microadenoma, 27 macroadenoma. Initial remission rates were: microadenoma 89% (66/74), macroadenoma 63% (17/27). Initial non-remission occurred in 18 patients, ten macro- and eight microadenoma. Six of the 83 patients with initial remission have had recurrence of hypercortisolism requiring either repeat TSS or adjunctive therapy. At last follow-up, continuing remission rates are: microadenoma 90%, macroadenoma 74%; 14 (seven macro, seven micro) have persistent hypercortisolism. Macroadenoma ($P=0.003$) and tumour invasion beyond the pituitary ($P<0.001$) were associated with failure of initial remission and greater likelihood of late recurrence. Absence of tumour on pre-operative imaging was not associated with failure of initial remission.
Conclusions
Surgery by a dedicated neurosurgeon in a specialised pituitary centre gives excellent initial and long-term results for CD. Presence of adenoma extension beyond the pituitary and immediate post-operative ACTH and cortisol levels are highly predictive of long-term outcome.

DOI: 10.1530/endoabs.37.GP.22.02

GP.22.03

Impact of preoperative magnetic resonance in surgical care of patients with Cushing's disease

Daniela Guelho[1], Diana Martins[1], Isabel Paiva[1], Luis Cardoso[1], Nuno Vicente[1], Diana Oliveira[1], Margarida Balsa[2] & Francisco Carrilho[1]
[1]Endocrinology, Diabetes and Metabolism Department of Coimbra Hospital and University Centre, Coimbra, Portugal; [2]Endocrinologia, Diabetes and Nutrition Department of Baixo Vouga Hospital Centre, Aveiro, Portugal.

Introduction
Cushing's disease (CD) is a rare disorder caused by an ACTH-secreting pituitary adenoma. Transsphenoidal surgery (TSS) is the recommended first-line treatment. However, an equivocal or even normal preoperative MRI can preclude the surgical management and the outcome of these patients.
Objectives
Evaluate the relationship between preoperative MRI and TSS efficacy in patients with CD.
Methods
Retrospective cohort study of patients with CD followed in our centre between 1977 and 2013 ($n=84$). Patients who lost follow-up or with insufficient data on their personal records were excluded ($n=51$). Statistical analysis: SPSS (21).
Results
Thirty three patients, 29 (87.9%) women, with a median of 33 years (24–70) were included. All patients underwent TSS as first treatment option and were followed postoperatively during a median period of 8 years (1–28). Patients were divided in: Group A ($n=19$), cured patients; and Group B ($n=14$), patients with persistent ($n=3$) or recurrent ($n=11$) CD within a median of 12 months. No significant demographic and clinical differences were recorded between the two groups. Group B patients presented a greater frequency of non-diagnostic preoperative images (28.6 vs 10.5%). And, in patients with a precisely visualized pituitary lesion ($n=27$), those of Group A presented significant lower tumour diameters (8.4 vs 13.9 mm, $P<0.01$), a greater number of pituitary micro-adenoma (68.4 vs 35.7%, $P<0.05$), and none invasive macroadenoma (0% vs 21.4%) compared to Group B patients. All patients with non-diagnostic preoperative MRI ($n=6$) performed inferior petrosal sinus sampling (IPSS), with identification of lateralization of ACTH secretion in all patients (2/2) of Group A and one patient (1/4) of Group B. A pituitary adenoma (confirmed by pathological examination) was found in 84.2% patients of Group A but only in 50% of Group B.
Conclusions
Precise preoperative localisation of a corticotroph adenoma, particularly a microadenoma, in preoperative MRI was associated with a greater efficacy of TSS and a higher probability of cure. Performance of IPSS can be useful in patients with non-diagnostic preoperative MRI.

DOI: 10.1530/endoabs.37.GP.22.03

GP.22.04

Long-term (5 years) treatment of Cushing's disease with pasireotide

Stephan Petersenn[1], Luiz R Salgado[2], Jochen Schopohl[3], Lesly Portocarrero-Ortiz[4], Giorgio Arnaldi[5], André Lacroix[6], Shoba Ravichandran[7], Albert Kandra[8], Teresa Bagulho[7] & Beverly MK Biller[9]
[1]ENDOC Center for Endocrine Tumors, Hamburg, Germany; [2]Division of General Internal Medicine, Hospital das Clínicas, University of São Paulo Medical School, São Paulo, Brazil; [3]Medizinische Klinik IV, University of Munich, Munich, Germany; [4]Department of Neuroendocrinology, National Institute of Neurology and Neurosurgery, Mexico City, Mexico; [5]Division of Endocrinology, Polytechnic University of Marche Region, Ancona, Italy; [6]Division of Endocrinology, Centre hospitalier de l'Université de Montréal, Montreal, Quebec, Canada; [7]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; [8]Novartis Pharma AG, Basel, Switzerland; [9]Neuroendocrine Clinical Center, Massachusetts General Hospital, Boston, Massachusetts, USA.

Background
In a large 12-month Phase III study, pasireotide led to rapid and sustained decreases in UFC and provided clinical benefit in patients with Cushing's disease. Here, we report data following an open-label, open-ended extension.
Methods
162 patients with persistent/recurrent or *de novo* Cushing's disease were randomized in the core study. 58 patients with mean UFC ≤ ULN or clinical benefit at month 12 entered the extension. Dose titration was permitted at the investigators' discretion (300–1200 μg s.c. bid). Efficacy data are presented for those patients who attended the visit at month 60; safety data are presented up to study end for all randomized patients.
Results
16 and seven patients were ongoing at months 60 and 72, respectively; maximum exposure was 76.6 months. For patients who reached month 60, percentage change in median UFC (range) from core baseline was −82.6% (−96.5% to 324.0%; $n=16$) and −81.8% (−94.9% to 3.4%; $n=15$) at months 12 and 60, respectively; of these patients, 10/16 and 11/16 had UFC ≤ ULN at months 12 and 60, respectively. Percentage change in median ACTH (range) was −34.7% (−72.0% to 66.7%; $n=16$) at month 12 and −8.3% (−68.0% to 100.0%; $n=16$) at month 60. Improvements in clinical signs, including systolic and diastolic blood pressure, weight, BMI, and total cholesterol level, were observed by month 6 and were sustained up to month 60. The most common AEs reported from core baseline until study end were diarrhoea (58.6%), nausea (53.7%), hyperglycaemia (41.4%), and cholelithiasis (32.7%); diabetes mellitus was reported in 22.2% of patients.
Conclusions
Initial reductions in UFC and improvements in clinical signs were maintained over 5 years of pasireotide treatment. No new safety signals were reported during long-term treatment. Results from this study suggest that pasireotide may be effective in the long-term treatment of Cushing's disease.
Disclosure
This work was supported by Novartis.

DOI: 10.1530/endoabs.37.GP.22.04

GP.22.05

Effects of osilodrostat (LCI699) on cytochrome P450 enzymes in healthy volunteers indicates a low drug–drug interaction potential

Lillian Ting[1], Anadya Prakash Tripathi[2], Christelle Darstein[3], Tracy White[1] & Nicholas Sauter[1]
[1]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; [2]Novartis Healthcare Pvt Ltd, Hyderabad, Telangana, India; [3]Novartis Pharma AG, Basel, Switzerland.

Introduction
In vitro assessments of osilodrostat (LCI699), a potent oral inhibitor of 11β-hydroxylase suggested potential drug–drug interactions (DDIs) with cytochrome P450 (CYP) enzyme metabolism. This clinical study evaluated the effect of osilodrostat on the pharmacokinetics (PK) of CYP1A2, CYP2C19, CYP2D6, and CYP3A4 probe substrates, caffeine, omeprazole, dextromethorphan, and midazolam, respectively.
Methods
A single-centre, open-label, Phase I, DDI study in healthy adult volunteers ($N=20$; male/female = 10/10). Day 1: A single dose of probe substrates (cocktail approach; caffeine (100 mg), omeprazole (20 mg), dextromethorphan (30 mg), and midazolam (2 mg)) was administered; PK assessments were done over 48 h. Day 2–7: 6-day washout period. Day 8: a single dose of osilodrostat 50 mg was administered followed by a single dose of probe substrates 0.5 h later. PK assessments were conducted over 48 h.
Results
AUC_{last} geometric mean ratio (GMR) and 90% CI of probe substrate exposure with osilodrostat administration were 2.33 (2.10–2.59), 1.91 (1.74–2.11), 1.48 (1.34–1.63), and 1.50 (1.41–1.60); AUC_{∞} GMR (90% CI) were 2.54 (2.34–2.75), 1.86 (1.61–2.15), 1.54 (1.40–1.69), and 1.50 (1.41–1.59) for caffeine, omeprazole, dextromethorphan and midazolam, respectively. C_{max} GMR (90% CI) for the change in substrate exposure was 1.07 (0.988–1.15), 1.61 (1.40–1.84), 1.35 (1.21–1.50), and 1.47 (1.32–1.62) for caffeine, omeprazole, dextromethorphan and midazolam, respectively. CYP1A2 and CYP2C19 are moderately inhibited and CYP2D6 and CYP3A4 are weakly inhibited by osilodrostat; exposures of probe substrates increased by ∼2.5-, ∼2.0-, ∼1.5-, and ∼1.5-fold, respectively.
Conclusions
It is reassuring that CYP3A4 (most clinically important CYP enzyme) was only weakly inhibited by osilodrostat 50 mg single dose, which covers the daily exposure of the maximum dose of 30 mg currently used in clinical trials. In a Phase II study, osilodrostat ≤10 mg twice-daily normalised urinary free cortisol levels in most patients with Cushing's disease; hence osilodrostat is unlikely to have a clinically relevant impact on the exposures of other medications cleared by CYP3A4.
Disclosure
This work was supported by Novartis.

DOI: 10.1530/endoabs.37.GP.22.05

GP.22.06

A specific nursing educational programme in patients with Cushing's syndrome

M Antonia Martínez-Momblán[1,2,5], Nuria Porta[4], Carmen Gómez[4], Julia Esteve[1,2], Alicia Santos[2,3], Inmaculada Úbeda[6], Irene Halperin[7], Beatriz Campillo[1,2], Montserrat Guillaumet[1,2], Susan M Webb[2,8] & Eugenia Resmini[2,3]
[1]Hospital Sant Pau, University School of Nursing, Barcelona, Spain; [2]Universitat Autónoma de Barcelona (UAB) 08193 Bellaterra (Cerdanyola del Vallès), Barcelona, Spain; [3]Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBER-ER), Unit 747, ISCIII, Barcelona, Spain; [4]Department of Statistics and Operations Research, Universitat Politècnica de Catalunya (UPC), Barcelona, Spain; [5]Intensive Care Departament, Hospital Sant Pau, Barcelona, Spain; [6]Departament of Nursing. Universitat de Barcelona, Barcelona, Spain; [7]Department Endocrinology, Hospital Clinic, Universitat de Barcelona, Barcelona, Spain; [8]Endocrinology/ Medicine Department, Hospital Sant Pau, IIB Sant Pau, Barcelona, Spain.

Context
Cushing's syndrome (CS) is a rare endocrine disease, due to cortisol hypersecretion. CS patients have several comorbidities, often still present after biochemical cure. There are no specific nursing healthcare programs to address this disease and achieve improved health related quality of life (HRQoL). Thus, an educational nursing intervention in these patients, through the development and promotion of specific educational tools, appears to be justified.
Objective
To assess the effectiveness of an educational nursing programme in CS patients to improve HRQoL, clinical parameters, level of pain and physical activity, patterns of rest and use of health resources.
Patient and methods
A prospective, randomized study was conducted in two reference hospitals for CS. Sixty-one patients (mean age 47 ± 12.7 years, 83.6% females) were enrolled and divided into two groups: an 'intervention' group where educational sessions were performed over nine months and a 'control' group, without these sessions. Specific questionnaires were used at the beginning and end of the study.
Results
After the educational sessions, the intervention group had a better score in Cushing QoL ($P<0.001$), improved level of pain ($P<0.05$), physical activity ($P<0.01$) and healthy lifestyle ($P<0.0001$) compared to the control group. A correlation between the Cushing QoL questionnaire score and improvement in pain ($P<0.05$), physical activity ($P<0.01$) and sleep ($P<0.01$) was observed.
Conclusions
This educational nursing program improved HRQoL, physical activity, healthy lifestyle and promoted adherence to therapy and better sleep patterns in CS patients, reducing health resources consumption. The brief nature of the programme makes it a good candidate to be used in patients with CS.
Disclosure
M[a] Antonia Martínez-Momblán received an unrestricted grant from Novartis as an investigator initiated study. The other authors have nothing to disclose.

DOI: 10.1530/endoabs.37.GP.22.06

GP.22.07

Neurosurgery outcome in patients with Cushing's disease with and without visualised pituitary adenoma on MRI, who underwent inferior petrosal sinus sampling

Zhanna Belaya, Patimat Khandaeva, Ludimila Rozhinskaya, Aleksandr Vorontsov, Ivan Sitkin, Andrey Grigoriev, Oksana Ivashenko, Larisa Dzeranova & Galina Melnichenko
Endocrinology Research Centre, Moscow, Russia.

Objective
To estimate the outcome of neurosurgery in patients with Cushing's disease (CD) with and without pituitary adenoma visualisation on MRI.
Material and methods
Patients with confirmed CD (11.2008–11.2014) by both inferior petrosal sinus sampling (IPSS) and histological evaluation after neurosurgery were enrolled into the study. Subjects were referred for IPSS because of non-visualised pituitary adenoma or contradictory results of non-invasive tests. Remission of Cushing's disease was confirmed in the event of development of adrenal insufficiency or normalisation of serum cortisol and 24 h urinary free cortisol (24hUFC) levels along with clinical remission at least during 3–6 months after neurosurgery. MRI was performed using Siemens Magnetom Harmony 1.0 T.
Results
A cohort of 113 (88 female) consecutive patients with CD confirmed by IPSS was enrolled, median of age (Q25–Q75) – 36 (27–50) years old; 24hUFC – 1903 (922–4219) nmol/24h; ACTH – 89.5 (60–135) pg/ml. In 51 cases pituitary adenoma was not visualised on MRI with gadolinium, 33 subjects were referred for IPSS because of adenoma ≤ 6 mm, 29 patients underwent IPSS due to negative for CD non-invasive tests. After the first neurosurgery remission was not achieved in 15 (29.4%) patients out of 51 without visualised adenoma on MRI; and in 9 (17.3%) cases out of 62 patients with visualised pituitary adenoma $P=0.066$ OR- 2.45 (0.97–6.21).
Conclusion
Remission rate after neurosurgery does not statistically significant differ between patients with CD with non-visualised pituitary adenoma on MRI and other patients with CD initially referred for IPSS.

DOI: 10.1530/endoabs.37.GP.22.07

Thyroid - diagnosis

GP.23.01

Evaluation of strain elastography for differentiation of thyroid nodules: results of a prospective multicentre study

Mireen Friedrich-Rust[1], Christian Vorlaender[2], Christoph F Dietrich[3], Wolfgang Kratzer[4], Wolfgang Blank[5], Andreas Schuler[6], Nathalie Broja[1] & Joerg Bojunga[1]
[1]Department of Internal Medicine 1, University Hospital Frankfurt, Frankfurt, Germany; [2]Department of General Surgery, Buergerhospital Frankfurt, Frankfurt, Germany; [3]Department of Internal Medicine 2, Caritas-Krankenhaus Bad Mergentheim, Bad Mergentheim, Germany; [4]Department of Internal Medicine I, University Hospital Ulm, Ulm, Germany; [5]Department of Internal Medicine 1, Klinikum am Steinberg, Reulingen, Germany; [6]Department of Internal Medicine, Helfenstein Klinik, Geislingen, Germany.

Introduction
Work-up of thyroid nodules remains challenging. At present, many patients with thyroid nodules are referred to surgery for diagnostic rather than therapeutic purposes. Therefore, the value of non-invasive diagnostic methods to optimize the selection of patients for surgery is needed. Strain elastography (SE) enables the determination of tissue elasticity and has shown promising results for the differentiation of thyroid nodules.
Methods
The aim of the present study was to evaluate the value of SE in a prospective multicentre study. A sample size calculation was performed when planning the study and the study was registered at clinical-trials.com. The study was approved by the local ethical committees of all participating centres, and written informed consent was obtained from all patients. All patients received an ultrasound (US) of the thyroid gland including colour doppler US and TIRADS classification. In addition all nodules were evaluated by strain elastography (Hitachi Medical System) using qualitative image interpretation of colour distribution (elastography score (ES) 1–4), strain value and strain ratio. Cytology and/or histology was used as reference method for all benign and histology only for all malignant nodules.
Results
Overall, 604 patients with 659 thyroid nodules (570 benign, 89 malignant) from six centres across Germany were included in the final analysis. Sensitivity, specificity, NPV, PPV, +LR were 22%, 74%, 86%, 11%, 0.8 for colour Doppler vascularization pattern 3–4; 79%, 40%, 92%, 17%, 1.3 for TIRADS; 69%, 74%, 92%, 36%, 2.66 for SE-ES; 58%, 81%, 92%, 32%, 3.0 for SE-strain value (cut-off 0.165); 60%, 78%, 92%, 31%, 2.7 for SE- strain ratio (cut-off 0.376), respectively. The diagnostic accuracies were 70% for TIRADS, 75% for SE-ES, 72% for SE-strain value, and 71% for strain ratio, respectively. No significant difference was found between these diagnostic accuracies.
Conclusions
Strain elastography as an additional ultrasound tool improves the diagnostic value of ultrasound for the exclusion of malignant thyroid nodules. Qualitative and semiquantitative elastography scores are comparably good.
Disclosure
This work was supported by Hitachi Medical Systems by providing ultrasound machines to some participating centers.

DOI: 10.1530/endoabs.37.GP.23.01

GP.23.02

Accuracy of sentinel lymph node biopsy in papillary thyroid carcinoma in decision for selective lateral neck dissection

Ivan Markovic[1,2], Marko Buta[1], Merima Oruci[1], Igor Djurisic[1], Nada Santrac[1], Gordana Pupic[1], Andjela Babic[1], Marija Markovic[1] & Radan Dzodic[1,2]
[1]Institute of Oncology and Radiology of Serbia, Belgrade, Serbia; [2]Medical Faculty University of Belgrade, Belgrade, Serbia.

Introduction
The incidence of occult lymph node metastases (LNM) in papillary thyroid carcinoma (PTC) reaches 80%, still their surgical management in clinically node negative (cN0) patients remains controversial and ranges from 'wait and see' principle to prophylactic dissections of both central and lateral neck compartments. This encouraged some authors to apply the concept of sentinel lymph node biopsy (SLNb) in PTC. Our aim to investigate if SLNb using methylene blue dye is accurate in detection of LNM in lateral neck compartment and may help in decision for selective modified lateral neck dissection in cN0 patients with PTC.
Study design
Study included 153 cN0 patients with PTC. All underwent total thyroidectomy with prophylactic central neck dissection and SLNb of lateral lymph nodes using methylene blue dye with selective modified lateral neck dissection in metastatic SLNs.
Results
Over 80% of patients had pT1 tumours, including 57% of microcarcinoma. Neck LNM were histologically verified in 40.9% of cases. Central neck compartment LNM were predictive for lateral LNM in 80.5% of cases. Predictive factors for LNM were: male gender, patients younger than 45 years, tumours greater than 1 cm, capsular and vascular tumour invasion. Our method enabled detection of metastases in 21% of SLN in lateral neck compartment, which were over 50% predictive of metastasis to other lateral lymph nodes. SLN identification rate (IR) was 91.81%. Sensitivity, specificity, positive and negative predictive value were 85.7, 96.7, 88.3 and 95.9% respectively. The overall accuracy of the method was 94.3%, with 91.2% probability of repeating the results in the second specimen (ROC AUC, 95% CI; 84.2–98.3%).
Conclusion
The proposed method of SLN biopsy is feasible, safe and accurate in detection of additional LNM in the lateral neck compartment and may help in decision for selective modified lateral neck dissection in cN0 patients with PTC.

DOI: 10.1530/endoabs.37.GP.23.02

GP.23.03

Incremental value of serial preablative thyroglobulin measurements in identifying distant metastatic differentiated thyroid cancer

Teng Zhao[1,2], Jun Liang[2], Yansong Lin[1], Xiaoyi Li[1], Tianjun Li[2] & Ke Yang[1]
[1]Peking Union Medical College Hospital, Beijing, China; [2]The Affiliated Hospital of Qingdao University, Qingdao, China.

Introduction
Thyroglobulin plays a vital role in the follow-up of patients with differentiated thyroid carcinoma (DTC) after thyroidectomy combined with radioiodine (RAI) ablation. As to preablative stimulated thyroglobulin (ps-Tg), though several studies have manifested its potential in identifying distant metastatic DTC (DM-DTC), it remains unclear whether a single ps-Tg is sufficient for predicting DM-DTC. This retrospective study was aimed to evaluate the utility of serial ps-Tg measurements in identifying DM-DTC.
Methods
A series of ps-Tg, thyroid-stimulating hormone (TSH) and anti-Tg antibody (TgAb) was measured in 317 consecutive DTC patients before RAI administration, among which data collected at the first time were marked as Tg1, TSH1 and TgAb1, respectively, while as Tg2, TSH2 and TgAb2 at the last time. Patients were divided into two groups as M1 ($n=72$) and M0 ($n=245$) according to the presence of DM or not. Parameters derived from the change in ps-Tg including ΔTg (Tg2-Tg1), $\Delta Tg'$ (Tg2/TSH2-Tg1/TSH1) and ΔTg/ΔTSH (ΔTg/(TSH2-TSH1)) were calculated and further combined with an actual or corrected value of ps-Tg (Tg1, Tg2, Tg1/TSH1 or Tg2/TSH2). All the independent and combined parameters were tested for diagnostic performance in identifying DM-DTC.
Results
Higher Tg1, Tg2, Tg1/TSH1, Tg2/TSH2 and wider amplitudes of ΔTg, $\Delta Tg'$, ΔTg/ΔTSH were observed in M1 (all $P<0.01$). Tg2 and Tg2/TSH2, with corresponding areas under ROC curves (AUC) of both 0.947, were more accurate than Tg1 and Tg1/TSH1. ΔTg/ΔTSH manifested the highest accuracy (88.64%) and specificity (90.20%) among the three parameters of preablative changes, with a diagnostic range of $-0.40\sim0.41$ ng/μIU. Moreover, the diagnostic performance was further improved with a larger AUC (0.951) by combing ΔTg/ΔTSH with Tg2/TSH2.
Conclusions
Serial ps-Tg measurements hold incremental value in identifying DM-DTC. ΔTg/ΔTSH in conjunction with Tg2/TSH2 is a favorable indicator for DM-DTC as well as a feasible approach to assist in preablative assessment and decision-making.
Disclosure
This work was supported by the Ministry of Health Industry Special Scientific Research Projects of China (201202012) and the National Natural Science Foundation of China (30970850).

DOI: 10.1530/endoabs.37.GP.23.03

GP.23.04

Impact of antithrombotic and/or anticoagulant treatment in cytological results of thyroid fine-needle biopsy

Carlos Arana Molina, Alberto Torres Cuadro, Natividad González Rivera, Clara García García, Virginia Hernando Jiménez, Luna Florencio Ojeda & Tomás Martín Hernández
Endocrinology and Nutrition Clinical Administration Unit, Virgen Macarena-Virgen del Rocío University Hospitals, Seville, Spain.

Introduction
Fine-needle aspiration biopsy (FNAB) of the thyroid gland is an accurate diagnostic test used routinely in the initial evaluation of nodular thyroid disease. A sizeable subset of patients are found to be taking antithrombotic and/or anticoagulant (AT/AC) medications. This creates a dilemma for the endocrinologist, who must weigh the risk of withholding these medications (and the associated potential benefit of diagnosis) against the perceived increased risk of iatrogenic bleeding.
Material and methods
We examined records of patients who underwent ultrasound-guided fine needle aspiration biopsy (US-FNAB) of thyroid nodules from the whole period 2012–2014, in order to determine whether there was a significantly increased incidence of bleeding complications in patients on AT/AC medications (test group) compared to patients not receiving AT/AC therapy (control group). All the studies were performed by the same experienced operator and cytopathologist team. The χ^2 test was used to assess statistically significant differences between test group and control group.
Results
A total of 83 patients (9.09%) were taking AT/AC medications without preprocedural interruption. Five US-FNAB-related hematomas (0.5%) occurred. Three hematomas developed in patients on AT/AC treatment, and two hematomas developed in patients who did not take AT/AC medications ($P=0.0014$). Twenty-four patients in the test group (40.6%) were labelled as 'nondiagnostic' cytology, vs 84 patients in the control group (10.1%) ($P<0.0001$).
Conclusion
Our results revealed an increased incidence in 'non diagnostic' or 'unsatisfactory' cytology in patients on AT/AC treatment, finding not described in previous studies until now. This could be related to a higher rate of cytological artifacts associated with lower blood coagulability. Our results also showed an increased bleeding risk in patients on AT/AC treatment. Despite this fact, most of studies argue that US-FNAB may be performed safely on a patient taking standard doses of aspirin or anticoagulants.

DOI: 10.1530/endoabs.37.GP.23.04

GP.23.05

Comparison of cytopathology vs thyroglobulin measurement in fine-needle aspiration biopsy in patients with differentiated thyroid cancer

Ahmet Kaya, Mustafa Kulaksizoglu & Feridun Karakurt
Necmettin Erbakan University, Meram Medical Faculty Internal Medicine, Konya, Turkey.

Aim
Differentiated thyroid cancer (DTC) is the most commonly seen endocrinological tumour. During the follow up of DTC, serum thyroglobulin (TG) levels, neck ultrasound, fine needle aspiration biopsy (FNAB) of the suspicious lymph nodes are important tools. TG washout of the suspicious lymph node as well as the FNAB can detect metastasis and recurrences earlier. In this study we aimed to show the diagnostic role of TG washout of suspicious lymph node FNAB which is not routinely done.
Methods
Totally 80 DTC patients that had suspicious lymph nodes during the follow up after thyroidectomy and radioactive ablation were retrospectively evaluated. All of patients' FNAB and TG washouts were done. Patients that underwent an operation thereafter were also evaluated according to the pathology.
Results
Totally 80 papillary thyroid cancer (PTC) patients, 91 lymph nodes were evaluated. 22 patients were operated, the rest of the patients that needed operation did not accepted operation. In 16 patients; FNAB was malign and TG washout were positive and all these two predicted the operation pathology which was malign. In three patients FNAB was suspicious, TG washouts were negative but operation pathology was benign, Tg washout predicted the true benign pathology in these three patients. In three patients FNAB was benign but TG washouts were positive and operation pathology was malign and TG washout predicted the pathology. TG washout predicted benign disease in three and malign disease in three patients which FNAB showed the contrary
Conclusion
Our study showed that TG washout can be used with adjunct to FNAB during the follow up of DTC patients that had already operated and received radioactive ablation especially in patients with suspicious lymph nodes on follow up neck ultrasounds. TG washout can aid in diagnosing recurrences and metastasis earlier and can increase the survey of the disease.

DOI: 10.1530/endoabs.37.GP.23.05

GP.23.06

FDG-avidity of thyroid cancer does not predict clinical aggressiveness in PET incidentaloma

Jee Hee Yoon, Hee Kyung Kim & Ho-Cheol Kang
Department of Internal Medicine, Chonnam National University Medical School, Gwangju, Republic of Korea.

Objective
18F-FDG-avid differentiated thyroid cancers (DTC) have been known to behave more aggressively, especially in metastatic sites (flip-flop phenomenon). However, the clinical behaviour of DTC detected incidentally by FDG–PET (PET incidentaloma) has been sparsely reported. We wanted to know whether flip–flop phenomenon is applicable in PET incidentalomas.
Methods
165 DTC patients who underwent thyroid surgery and had pre-operative FDG–PET examination at Chonnam National University Hwasun Hospital between January 2006 and August 2013 were included in the study. We compare the clinical characteristics between screening PET–CT group (thyroid incidentaloma) and staging PET–CT group.
Results
129 DTC patients were FDG-avid and 36 patients non-FDG-avid. FDG avid PTC is more aggressive than FDG non-avid PTC on the clinico-pathologic findings. After removal of high-risk group (staging PET–CT group), thyroid PET–CT incidentaloma patients ($n=107$) were compared according to FDG avidity. Among thyroid PET–CT incidentaloma patients, FDG avid PTC group ($n=75$) revealed larger tumour size (0.97 ± 0.52 vs 0.61 ± 0.35, $P=0.001$), but extrathyroidal invasion (ETI), cervical lymph node metastasis, and distant metastasis is not different between FDG avid PTC group and FDG non-avid PTC group. A cumulative risk of cervical lymph node metastasis according to primary tumour size of FDG avid PTC group is not different from those of FDG non-avid PTC group ($P=0.394$).
Conclusions
DTC detected with FDG-avidity do not seem to behave aggressively, based on initial operative findings. FDG-avidity of DTC does not add to conventional risk factor assessment for initial therapeutic decision.

DOI: 10.1530/endoabs.37.GP.23.06

GP.23.07

Immunohistochemical tool for the diagnosis of benign and malignant follicular tumours

Esmeralda Castelblanco[1,2], Montserrat Martinez[3], Ma Dolores Santos[3], Verónica Mancikova[5], Mercedes Robledo[5], Xavier Matias-Guiu[3,4], Javier Maravall[3] & Didac Mauricio[1,2]
[1]Servicio de Endocrinología y Nutrición, Hospital Germans Trias i Pujol, Badalona, Catalunya, Spain; [2]Instituto de Investigación en Salud Germans Trias i Pujol, Badalona, Catalunya, Spain; [3]Instituto de Investigación Biomédica de Lleida, Universidad de Lleida, Lleida, Catalunya, Spain; [4]Servicio de Patología y Genética Molecular, Hospital Universitario Arnau de Vilanova, Lleida, Catalunya, Spain; [5]Centro Nacional de Investigaciones Oncológicas, Madrid, Catalunya, Spain.

Introduction
Follicular tumours of the thyroid gland include benign follicular adenomas, follicular carcinomas and the follicular variant of papillary carcinoma. Although, molecular markers are a promising area of research to differentiate thyroid neoplasms, there is ample room for improvement in the research and clinical applications in this field. Furthermore, the final diagnosis requires thyroid lobectomy. The present study examined whether a differential protein expression could provide an accurate tool to improve diagnosis in these tumours.
Design
The expression of 19 proteins was evaluated in 125 surgically removed thyroid tumours including 81 follicular adenomas (FA) and 44 malignant tumours (nine follicular carcinomas (FTC) and 35 follicular variant of papillary carcinomas (FVPTC)). Classification trees and scoring systems were constructed based on protein expression to generate models that could allow a differential diagnosis between benign and malignant tumours. Forty hyperplastic nodules (HN) were used to test the goodness of fitness of the generated models.
Results
The classification tree that better discriminated between benign and malignant nodules was APLP2 ($n=0$), RRM2 ($n>5$), PRC1c ($n\geq40$), APLP2c ($n\leq105$), and SIAH1 ($n\leq5$), with a sensitivity of 100% and a specificity of 98.8%. In HN, the sensitivity was 94.8%. The punctuation system model $4\times$(APLP2 ($n=0$))$+$ $2\times$(RRM2 ($n>5$))$+1\times$(PRC1c ($n\geq40$)) reached a sensitivity of 100% and a specificity of 71.3%.
Conclusion
Our findings support the potential of these models to improve not only the diagnosis of follicular thyroid tumours but also, the management and wellness of patients by reducing the number of exploratory surgeries. We are currently validating these results in an independent series.
Disclosure
This work was financed for Institute Carlos III (FIS PI11/1354).

DOI: 10.1530/endoabs.37.GP.23.07

GP.23.08

Clinical characteristics in sporadic and familial medullary thyroid carcinomas: worse outcome in sporadic cases even when disease stage at diagnosis is similar

Katerina Saltiki, Loukia Spanou, Sofia Kouki, Gianna Rentziou, Vasiliki Vasileiou, Eleni Anastasiou & Maria Alevizaki
Endocrine Unit, Department of Medical Therapeutics, Alexandra Hospital, Athens University School of Medicine, Athens, Greece.

Objectives
Medullary thyroid carcinoma (MTC) has varying clinical course with familial cases (fMTC) diagnosed earlier than sporadic ones (sMTC). We examined the presentation of these entities in our centre.
Methods
223 MTC patients (familial: 42.6%, males: 36.8%) were followed for 0.9–30 years (mean 6.23 ± 5.9, median 4.0 years). 44 (19.7%) fMTC patients were operated after genetic screening.
Results
Median age at diagnosis was for fMTC: 32.4 ± 16.3 years (range 4–73) and for sMTC: 52.4 ± 13.6 years (range 16–81, $P<0.001$). This difference remained when cases diagnosed after genetic screening were excluded ($P=0.001$). fMTC was more frequent in women than men (48.2% vs 32.9%, $P=0.018$). Capsular invasion, lymph node invasion, distant metastasis at diagnosis was similar. The size of sMTCs was more frequently ≥1.5 cm ($P=0.012$). Stage at diagnosis was more favorable in fMTCs (stages I and II: 60.4% vs 51.2%, stage III: 8.8% vs 23.2%, and stage IV: 42.1% vs 57.9%, $P=0.021$). Preoperative and postoperative calcitonin levels were significantly lower in fMTCs. fMTC had more frequently remission (62.9% vs 49.2%) and less frequently progressive disease (9% vs 36.3%, $P<0.001$).

After excluding patients diagnosed through genetic screening, no difference in stage at diagnosis was observed. Tumour size and postoperative calcitonin levels did not differ. Outcome was more favorable in fMTC compared to sporadic (remission: 56.3% vs 48.8%, stable: 29.2% vs 14.6%, and disease progression: 14.6% vs 36.6%, $P=0.008$). The 10-year probability of lack of progression of disease differed significantly between familial and sporadic MTCs (85.4% vs 63.4%, Kaplan–Meier analysis, $\chi^2=19.01$, $P<0.001$).
Conclusions
After excluding those diagnosed through genetic screening, although stage at diagnosis is currently similar and does not differ between familial and sporadic cases, disease outcome remains worse in sporadic MTCs. Women may have increased awareness for genetic screening in familial cases.

DOI: 10.1530/endoabs.37.GP.23.08

GP.23.09

Low/undetectable pre-ablation thyroglobulin in well-differentiated thyroid cancer patients with positive post-ablative ^{131}I whole body scans: causes and consequences

Daniela Guelho[1], Fernando Albán[2], Miguel Melo[1], Cristina Ribeiro[1], Isabel Paiva[1], Carolina Moreno[1], Nuno Vicente[1], Luis Cardoso[1], Diana Martins[1], Diana Oliveira[1], Margarida Balsa[3], Gracinda Costa[2] & Francisco Carrilho[1]
[1]Endocrinology, Diabetes and Metabolism Department, Coimbra Hospital and University Centre, Coimbra, Portugal; [2]Nuclear Medicine Department, Coimbra Hospital and University Centre, Coimbra, Portugal; [3]Endocrinology, Diabetes and Nutrition Department, Baixo Vouga Hospital Centre, Aveiro, Portugal.

Introduction
In patients with well-differentiated thyroid cancer (DTC) low/undetectable thyroglobulin (Tg) at time of remnant ablation usually reflects a complete previous surgery. However, in a small percentage (6.3–16%) it can represent false negative values.
Objectives
Evaluate the frequency of patients with low/undectable Tg at time of remnant ablation with locoregional or distant lesions at post-ablative ^{131}I whole body scan (WBS) and the influence of Tg levels in long-term outcome.
Methods
Retrospective analysis of all patients with DTC submitted to ablative ^{131}I treatment in our centre. Included: patients with a stimulated Tg <5 ng/ml (measured at time of remnant ablation) and locoregional or distant uptake at post-ablative ^{131}I WBS, performed 6–7 days after. Excluded: patients with TSH <30 mUI/ml after thyroid hormone withdrawal or with a follow-up <6 months. Statistical analysis: SPSS (21).
Results
Of 967 patients, 211 (21.8%) were included (178♀; 33♂). Ninety-two (43.6%) presented anti-Tg antibodies. Only patients with negative anti-Tg antibodies ($n=119$) were considered at subsequent analysis. In those, Tg was lower if lymphocytic infiltrate ($P<0.05$) or abundant solid areas ($P<0.05$) present at histopathological evaluation. Post-ablative ^{131}I WBS showed thyroid bed (73.3%), laterocervical (5.9% unilateral and 16.8% bilateral), supraclavicular (0.8%), mediastinal (1.6%), and pulmonar (1.6%) uptake. During a follow-up of 8 ± 4.8 years, 17 (14.3%) patients showed persistence/recurrence of the disease: eight local and nine distant. The probability of persistence/recurrence was significantly higher if lymph node metastasis (OR=11.8; $P<0.01$) or extrathyroid uptake at post-ablative ^{131}I WBS (OR=20.8; $P<0.01$). Disease-free survival was inversely correlated with Tg ($\rho=-0.59$; $P<0.01$), being significantly higher in patients presenting undectable Tg ($P<0.05$).
Conclusion
A fifth of DTC patients presented low/undectable Tg at time of remnant ablation with uptake (locoregional or distant) at post-ablative ^{131}I WBS. In about half was justified by anti-Tg antibodies. In the others, may be related to the presence of microscopic lesions or specific histopathological features. In these patients, low/undectable Tg did not exclude risk of persistence/recurrence, but it seems related with disease-free survival. This study also highlights the importance of post-ablative ^{131}I WBS in the evaluation of these patients.

DOI: 10.1530/endoabs.37.GP.23.09

Thyroid – genetics

GP.24.01

Prox1 transcription factor is differentially expressed in thyroid cancer and contributes to the regulation of invasion and migration of thyroid cancer cells

Magdalena Rudzinska[1], Damian Gawel[1], Kamila Karpinska[1], Miroslaw Kiedrowski[2], Tomasz Stepien[3], Magdalena Marchlewska[3], Wanda Krasuska[1], Joanna Ledwon[1], Maria Macios[1], Dariusz Lange[4] & Barbara Czarnocka[1]
[1]Department of Biochemistry and Molecular Biology, The Center of Postgraduate Medical Education, Warsaw, Poland; [2]Department of Oncology and Hepatology, Clinical Hospital Ministry of Interior, Warsaw, Poland; [3]Department of General and Endocrinological Surgery, Copernicus Memorial Hospital, Warsaw, Poland; [4]Department of Tumor Pathology, Institute of Oncology Gliwice Branch, Maria Sklodowska-Curie Memorial Cancer Center, Gliwice, Poland.

Introduction
The differentiated thyroid cancer (DTC) is the most frequent endocrine malignancy with the incidence increasing worldwide. Although, DTCs are considered to be mostly indolent lesions, the proportion of patients develop metastases. Therefore, identification of molecular factors that are involved in thyroid tumour progression might help to better understand the mechanism of thyroid cancer metastasis. In the present study we examine the role of the transcription factor prospero homeobox 1 (Prox1) in DTC biology. Prox1 is the nuclear transcription factor expressed specifically in LEC cells and as recently shown, also in several human cancers.
Methods
We performed studies using follicular and papillary thyroid cancer derived cell lines. The Prox1 protein and transcript expression levels and its localization were determined using molecular biology methods: Q-RT-PCR, gene silencing, western blot, and immunocytochemistry. To determine the Prox1 role in regulating the hallmarks of malignant cell phenotype we analysed migration, invasion, anchorage-independent growth, proliferation, cell cycle, apoptosis, and adhesion upon *Prox1* gene silencing.
Results
We observed significant difference in the Prox1 expression between FTC and PTC derived cancer cell lines. Prox1 transcript and protein levels were overexpressed in follicular cancer cell lines FTC133 and CGTH when compared with PTC cell lines. Moreover, the protein was localized in the nucleus or both the nucleus and cytoplasm respectively. RNA-i knockdown of Prox1 suppressed cellular migration, invasion and anchorage independent growth of FTC-133 cells, whereas proliferation, cell cycle and adhesion were unchanged. Moreover, Prox1 down regulation modified of FTC133 cells shape by actin cytoskeleton reorganization.
Conclusion
Our data suggest an important role for transcription factor Prox1 in i) the regulation of hallmarks of the malignant cell phenotype as migration and invasive capacity and ii) in the actin cytoskeleton remodelling in thyroid cancer cells. Further on-going studies will clarify the role of Prox1 in thyroid cancer cells dissemination.

DOI: 10.1530/endoabs.37.GP.24.01

GP.24.02

In papillary thyroid cancer *TERT* promoter mutations have a worst impact on outcome than *BRAF* mutations

Marina Muzza[2], Carla Colombo[2], Maria Carla Proverbio[1], Stefania Rossi[3], Delfina Tosi[3], Michela Perrino[2], Simone De Leo[2], Valentina Cirello[1], Gaetano Bulfamante[3], Leonardo Vicentini[4] & Laura Fugazzola[1]
[1]Endocrine Unit, Department of Pathophysiology and Transplantation, Fondazione IRCCS Ca' Granda, University of Milan, Milan, Italy; [2]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; [3]Division of Pathology, Department of Health Sciences, San Paolo Hospital, University of Milan, Milan, Italy; [4]Endocrine Surgery Unit, Fondazione IRCCS Ca'Granda, Milan, Italy.

TERT promoter mutations (chr5: 1 295 228C>T e chr5: 1 295 250C>T) were recently described in thyroid tumors, with a prevalence ranging 8–25% in papillary thyroid cancer (PTC). We and others reported that these mutations strongly associate with a poor outcome in differentiated thyroid cancers. Aim of

the present study was to further investigate the prognostic role of both *TERT* promoter ($TERT^{MUT}$) and $BRAF^{V600E}$ mutations in a larger series of 216 PTCS with a long follow-up (median: 77 months). We also evaluated the possible additive effect on the outcome of the coexistence of the two genetic alterations. Genetic data were obtained by direct sequencing and were correlated with full clinical data. The prevalence of $TERT^{MUT}$ and of $BRAF^{V600E}$ was 12 and 35% respectively. Ten cases (5%) harbored both $TERT^{MUT}$ and $BRAF^{V600E}$. Cases with a $TERT^{MUT}$ alone, but not those with $BRAF^{V600E}$ alone, were significantly associated with older age at diagnosis and poorer outcome ($P=0.04$ for both). No differences in the outcome were noted between cases with the $TERT^{MUT}$ alone or with the coexistence of $TERT^{MUT}$ and $BRAF^{V600E}$. In conclusion, *TERT* mutations were found to have a 12% prevalence in PTCs and were confirmed to be a major indicator of poor prognosis. On the other hand, $BRAF^{V600E}$ was not associated with the outcome, consistent with data previously obtained in our series. Moreover, the outcome was not different among tumors with isolated $TERT^{MUT}$ and those with coexistent mutations ($TERT^{MUT}/BRAF^{V600E}$), indicating that $BRAF^{V600E}$ does not confer an additional effect in the disease persistence.

DOI: 10.1530/endoabs.37.GP.24.02

GP.24.03

Evaluation of genetic background of sporadic medullary thyroid carcinomas

Vlasta Sykorova[1], Sarka Dvorakova[1], Josef Vcelak[1], Eliska Vaclavikova[1], Daniela Kodetova[2], Petr Lastuvka[3], Jan Betka[3], Petr Vlcek[4], Pavla Sykorova[4] & Bela Bendlova[1]
[1]Department of Molecular Endocrinology, Institute of Endocrinology, Prague, Czech Republic; [2]Department of Pathology and Molecular Medicine, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, Czech Republic; [3]Department of Otorhinolaryngology and Head and Neck Surgery, 1st Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, Czech Republic; [4]Department of Nuclear Medicine and Endocrinology, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, Czech Republic.

Objectives
Although, almost all patients with inherited medullary thyroid carcinomas (MTC) harboured *RET* proto-oncogene mutation, in patients with sporadic MTC, mutations in *RET* are detected only in half of cases. Thus still unknown genetic causes are responsible for half of sporadic MTC and it is necessary to search for another mutations.
Methods
DNAs from fresh frozen thyroid tissues of 27 sporadic MTC were extracted. The next-generation sequencing (NGS) approach was used to target 175 exonic regions of 26 genes involved in tumors. The samples were prepared using a TruSight Tumor panel (Illumina) and sequenced with a MiSeq sequencer (Illumina). Analysis of variants was performed by MiSeq Reporter Software and evaluated by Illumina VariantStudio Software. *RET* and *HRAS* genes were analysed separately using direct sequencing by CEQ 8000 (Beckman Coulter), because these two genes were not included in the panel.
Results
RET mutations were detected in 12 samples – mutation in exon 16 (Met918Thr) in eight patients and mutations in exon 10 and 11 (Cys618Ser, Cys620Ser, Cys630Ser, and 628–632del) in four patients. In four MTC tissues mutations in *HRAS* genes (codons 13 and 61) were detected. NGS revealed mutations in *KRAS* gene in codons 12 and 61 in three MTC patients. Futher, we identified missense mutation Thr273Asn in gene for hepatocyte growth factor receptor (MET) in the patient with mutation Gln61Arg in *HRAS* gene. Except this patient all mutations were presented exclusively.
Conclusions
In our cohort of sporadic MTC tissues, mutations were detected in 19 patients (70.3%) – *RET* mutations in 44.4% and RAS mutations in 25.9%. Except of known mutations in *RET* and *RAS* genes, the unknown variant in conserved sequence of *MET* gene was revealed which was identified as deleterious and possibly damaging in software SIFT and PolyPhen-2 respectively.
Disclosure
This work was supported by IGA MH CR (grant number NT13901-4) and MH CR (grant number DRO 00023761).

DOI: 10.1530/endoabs.37.GP.24.03

GP.24.04

Lymph node involvement using one-step nucleic acid amplification according to *BRAF* gene mutation status in patients with papillary thyroid carcinoma submitted to lymph node dissection

Carles Zafon, Oscar Gonzalez, Jordi Temprana, Gabriel Obiols, Amparo Garcia-Burillo, Xavier Serres, José María Balibrea, Joan Castell, Jordi Mesa & Carmela Iglesias
Hospital Universitari Vall d'Hebron, Barcelona, Spain.

Introduction
The relationship between the *BRAF* gene mutation in papillary thyroid cancer (PTC) and the presence of lymph node metastasis (LNM) is a subject of controversy.
Objective
To analyse the influence of BRAF mutation status in the characteristics of lymph nodes in patients with PTC submitted to lymph node dissection (LND).
Material and methods
Lymph nodes obtained from 20 patients (12 females, mean age 50 ± 15 years old), corresponding to 21 LND were evaluated. LNM were detected using the molecular technique one-step nucleic acid amplification (OSNA), that measures the number of copies of mRNA of cytokeratin 19 (CK19) as a marker. According to the presence/absence of *BRAF* gene mutation cases additional clinical, histological, and node related variables were studied.
Results
A total of 277 lymph nodes from 21 LND were evaluated. BRAF was positive in 13 patients. There were no significant differences in clinical and histological variables according to BRAF mutation. There were no differences in the total number of nodes dissected per patient. There were 67 nodes from BRAF-negative patients and 210 nodes from BRAF-positive patients. There were no significant differences in lymph node weight or size between BRAF-negative and BRAF-positive cases. LNM were detected in 88 nodes, 14 out of 67 (20.9%) in the BRAF-negative group and 74 out of 210 (35.2%) in the BRAF-positive patients ($P=0.03$). Finally, no significant differences were found in the total copy number of mRNA of CK19 between both groups.
Conclusion
The probability of LNM is higher among those lymph nodes with BRAF mutated tumours than in BRAF not mutated cases. However, there were no differences in morphological characteristics of dissected lymph nodes.

DOI: 10.1530/endoabs.37.GP.24.04

GP.24.05

Telomerase reverse transcriptase promoter mutation analysis on thyroid core needle biopsy

Marcella Callea[1], Anna Crescenzi[1], Pierpaolo Trimboli[2], Davide Cicciarella Modica[2], Chiara Taffon[1], Leo Guidobaldi[2], Silvia Taccogna[3], Alberto Rainer[1], Marcella Trombetta[1], Enrico Papini[3] & Giovanni Zelano[4]
[1]Campus Bio-Medico University Hospital, Rome, Italy; [2]Israelitico Hospital, Rome, Italy; [3]Regina Apostolorum Hospital, Rome, Italy; [4]Sacro Cuore Catholic University Hospital, Rome, Italy.

Introduction
Among molecular markers proposed to improve diagnosis of thyroid nodules, mutations in telomerase reverse transcriptase (TERT) promoter have been correlated to malignant tumors with highest recurrence and decreased patient's survival. This suggests an important role of TERT mutational analysis in the clinical diagnosis and management of thyroid cancer patients. In this study, we investigate the potential use of core needle biopsy (CNB) for the preoperative assessment of TERT mutational status and we correlate TERT status with BRAF mutation, definitive histology and post-operative TNM staging of the neoplasia.
Methods
The series included 50 thyroid nodules, retrospectively selected among 187 patients who underwent CNB due to an inconclusive fine-needle aspirate (FNA) report, during last 2 years at two different institutions in Rome. Selected cases consisted of 30 papillary thyroid carcinomas (PTC), one follicular carcinoma (FTC), nine follicular adenomas, and ten nodular hyperplasias. Core samples were processed for morphological and molecular analysis. TERT mutational analysis was performed by Sanger sequencing and *BRAF* gene was analysed by pyrosequencing.
Results
C228T TERT promoter mutation was found in 3/30 (10%) of PTC with prevalence of 17.6% among locally advanced PTCs. The only case of FTC, adenomas and hyperplastic nodules did not show the mutation. Mutated cases showed locally invasive PTC with multiple lymph-node metastases and, in one patient, with lung metastasis. All TERT mutated cases showed concomitant V600 BRAF mutation.

Conclusions
The present study demonstrates the feasibility of TERT promoter mutational analysis on thyroid CNB. This methodology consents to identify tumors with a worse outcome at the preoperative time on specimens evaluated for quality and representativeness. This information might be used to individualise treatment decisions, surgical options and follow-up design.

DOI: 10.1530/endoabs.37.GP.24.05

GP.24.06

Gene expression profiling in differentiated thyroid carcinoma

Sorina Schipor[1], Ana-Maria Niculescu[3], Dana Manda[1], Andra Caragheorgheopol[1], Sabina Oros[1], Susana Vladoiu[1], Oana Popa[1], Diana Paun[1,2] & Corin Badiu[1,2]
[1]National Institute of Endocrinology C. I. Parhon, Bucharest, Romania; [2]University of Medicine and Pharmacy Carol Davila, Bucharest, Romania; [3]Agilrom Scientific SRL, Bucharest, Romania.

Thyroid carcinoma is the most common endocrine malignancy and represents ~1% of all types of human cancer.
Objective
As the molecular pathogenesis of thyroid cancer still remains to be clarified, the goal of our study was to find new molecular markers that could improve the diagnostics, follow-up protocols, treatment outcome, prognosis and the quality of life of differentiated thyroid cancer patients.
Subjects and methods
Matched tumour and normal thyroid tissue samples were obtained from patients that have surgical cure for differentiated thyroid carcinoma after they gave their informed consent. RNA was extracted using the RNeasy Mini Kit from Qiagen and the quality was checked with the Infinite® 200 NanoQuant (Tecan) and with the 2100 Bioanalyzer (Agilent). 24 samples with RIN >7 were chosen for microarray gene expression analysis (six with classical papillary thyroid carcinoma and six with papillary thyroid carcinoma folicullar variant). Microarray analysis was performed following Agilent One-Color Microarray-Based Gene Expression protocol, ver 6.6, using SurePrint G3 Human Gene Expression arrays 8x60K v2.
Results
Using GeneSpring ver 12, we identified 25 genes and two long intergenic non-protein coding RNA (lincRNA 1140 and BROAD Institute lincRNA (XLOC_005062)/lincRNA (TCONS_00010536) down regulated in the tumour tissue compared with the normal one, P value <0.05 and fold change ≥ 2. When accounting for the two thyroid cancer types studied, we identified three genes up-regulated (COL13A1, EDA2R, and KLHDC8A) and eight down regulated (SLITRK5, CCL21, TFPI, TBX1, LOC389033, ADH1C, MMRN1, and F10) in both subtypes. The level of gene expression disregulation is much higher in the case of classical papillary thyroid carcinoma.
Conclusion
Gene expression is altered in papillary thyroid carcinoma. Our study identified three hyper-expressed genes and eight genes with low expression in tumoural tissue compared to normal one. Further studies are undergoing for gene expression data validation by qPCR.
Disclosure
This work was supported by UEFISCDI (grant number PN-II-PT-PCCA-2011-3.2, 135/2012).

DOI: 10.1530/endoabs.37.GP.24.06

GP.24.07

Combination of serum miRNA-190 and -95 is a powerful non-invasive tool in the differential diagnosis of thyroid nodules: preliminary data of a prospective series

Tania Pilli[1], Silvia Cantara[1], Giulia Busonero[1], Sandro Cardinale[1], Gabriele Cevenini[3], Guido Sebastiani[2], Francesco Dotta[1] & Furio Pacini[1]
[1]Department of Medicine, Surgery and Neuroscience, Siena, Italy; [2]Fondazione Umberto Di Mario ONLUS, Toscana Life Sciences, Siena, Italy; [3]Department of Medical Biotechnologies, University of Siena, Siena, Italy.

Background
MicroRNAs (miRNAs) are small non-protein encoding RNAs which negatively regulate gene expression. Tissue miRNA profiles may be useful to distinguish benign from malignant lesions. Recently, we have identified in the serum of a retrospective series of patients, with benign nodular goiter ($n=80$) and papillary thyroid cancer (PTC: $n=79$), two miRNAs (-190 and -95) that in combination (providing the risk of malignancy defined as pmiRNA) allow the differential diagnosis of thyroid nodules with great accuracy. This study was aimed to confirm the diagnostic accuracy of miRNA-190 and -95 in a prospective series of patients.
Methods
Blood samples were collected from 126 consecutive patients undergoing fine-needle aspiration cytology at our Institute. miRNAs were extracted from serum using the miRNeasy Serum/Plasma Kit (Qiagen), and reverse-transcribed using Megaplex Human microRNA RT primers pools v2.1 (Life Technologies). cDNA was then pre-amplified. Relative expression quantification was evaluated by the comparative cycle threshold (CT) method ($2^{-\Delta\Delta CT}$) (Rotor-gene Q, Qiagen). Endogenous miRNA-16 and miRNA-451 were selected as reference to normalize miRNA expression values.
Results
Based on cytology (following BTA guideline): the lesions were benign (Thy2) in 85/121 (70.2%) cases, suspicious for malignancy or malignant (Thy4/5) in 14/121 (11.6%), indeterminate (Thy3) in 16/121 (13.2%), and non diagnostic (Thy1) in 6/121 (5%). A subgroup of 48 patients underwent surgery and the lesions at histology were benign in 30/48 (62.5%) cases and malignant in 18/48 (37.5%). PmiRNA showed a high sensitivity (84%), specificity (93.5%), and diagnostic accuracy (90%) in PTC diagnosis. Moreover, by applying pmiRNA, we could have avoided two out of three unnecessary surgeries in patients with Thy3 cytology.
Conclusions
These preliminary data confirm that pmiRNA may be useful as a non-invasive diagnostic tool for the differential diagnosis of thyroid nodules, particularly in case of indeterminate lesions where pmiRNA role is promising but further studies are warranted.
Disclosure
PRIN No. 2010RNY8T_001; MOH-GR-2010-2321454.

DOI: 10.1530/endoabs.37.GP.24.07

GP.24.08

Identification of a LIN28B/miR-30a axis controlling thyroid cell invasion and proliferation

León Wert-Lamas & Pilar Santisteban
IIB Alberto Sols UAM–CSIC, Madrid, Spain.

The oncofoetal miRNA-binding protein LIN28B plays an important role in differentiation and cancer progression. Lin28B induces epithelial-mesenchymal transition, and it is considered as a bad prognostic marker in several tumours. The aim of this work was to study the effect and regulation of LIN28B on the thyroid cancer progression process. In a first approximation a miRNA targets computational predictions were performed with miRanda algorithm and we found that among others the miR-30a binds to the 3′ UTR of LIN28B. As previous results, obtained by next-generation sequencing expression analysis, performed in our laboratory showed that miR-30a is one of the most significantly miR subexpressed in thyroid cancer, we decided to focus on its role over LIN28B. miR-30a expression vector was transfected in 8505c and Cal62 cells; LIN28B in NThy-ori thyroid cells; and reporter construct containing LIN28B 3′ UTR in HeLa cells. The levels of mRNA and protein were determined by RT-qPCR and western blot. Invasion and proliferation assays were performed in Transwell® and TC20 cell counter, respectively, Lin28B protein expression was determined in 16 thyroid cancer cell lines and was correlated with RAS and BRAF mutations in ATC derived cells. Overexpression of miR-30a resulted in LIN28B, HMGA2, H-RAS, PI3Kβ, BCL2, and CDK6 mRNA and protein silencing, and in an increase in p27(Kip) protein levels in the nucleus. Inversely, LIN28B over-expressing cells showed a decrease in miR-30a levels and an increased expression of HMGA2 and H-RAS oncogenes. Furthermore, we observed that the LIN28B inhibition by miR-30a is specifically elicited through a direct binding to its 3′ UTR. The general outcome was a significant decrease in invasion and proliferation in miR-30a overexpressing cells and, conversely, an increase in these parameters in LIN28B overexpressing cells. These data suggest the existence of a LIN28B/30a axis, with a double negative feedback regulation, whose tumoural shift, leading to overexpression of LIN28B and silencing of miR-30a, widely contributes to thyroid cancer progression.
Disclosure
This work was supported by the Ministerio de Economia y Competitividad (SAF2013-44709R) and by the Comunidad de Madrid (S2011/BMD-2328-Tironet).

DOI: 10.1530/endoabs.37.GP.24.08

Thyroid - nodule

GP.25.01

Long-term results of US-guided high-intensity focused ultrasound treatment of benign thyroid nodules

Roussanka Kovatcheva[1], Jordan Vlahov[1], Julian Stoinov[2] & Katja Zaletel[3]
[1]Department of Thyroid and Metabolic Bone Disorders, University Hospital of Endocrinology, Sofia Medical University, Sofia, Bulgaria; [2]Department of Endocrine Surgery, University Hospital of Endocrinology, Sofia Medical University, Sofia, Bulgaria; [3]Department of Nuclear Medicine, Ljubljana University Medical Centre, Ljubljana, Slovenia.

Introduction
Thyroid nodules can be detected by ultrasound (US) in 20–30% of unselected populations. Various non-surgical techniques such as laser and radiofrequency ablation have been developed to reduce thyroid nodule size. High-intensity focused ultrasound (HIFU) ablation is a new, non-invasive method that has been shown recently. The aim of our study was to assess the long-term efficacy and safety of US-guided HIFU treatment of benign solid thyroid nodules.
Methods
In our prospective study, 14 patients, mean age 47.6 ± 11.2 years, were treated with US-guided HIFU system (EchoPulse, Theraclion) in one session and under conscious sedation. Thyroid nodule volume and volume reduction were established at baseline, 1, 3, 6, and 12 months after treatment. Adverse events were evaluated and pain related to treatment was rated on 0–100 mm visual analogue scale (VAS). Written informed consent was acquired from all patients.
Results
The mean energy applied per nodule volume was 3.7 ± 1.5 kJ/ml. The mean nodule volume decreased from 4.97 ± 2.54 to 3.56 ± 2.01 ml at 1 month, 2.84 ± 1.95 ml at 3 months, 2.55 ± 2.23 ml at 6 months, and reaching 2.35 ± 2.34 ml at 12 months follow-up. The mean nodule reduction was 29.5 ± 15.9% at 1 month ($P < 0.001$), 46.2 ± 18.5% ($P < 0.001$) at 3 months, and 52.8 ± 23.3% ($P < 0.001$) at 6 months follow-up. By the 12th month, the mean volume reduction was 55.7 ± 27.2% with a maximum of 95.4%. Transient subcutaneous oedema and mild skin redness were observed in two patients. VAS score was 26.1 ± 19.5 mm.
Conclusion
One session HIFU ablation is effective non-invasive treatment for benign thyroid nodules at long-term follow-up, without serious adverse events. Our results indicate that US-guided HIFU might become an alternative to surgery and other minimally invasive treatment techniques.
Disclosure
The device for US-guided HIFU treatment and financial support for the supplies were provided by Theraclion (Paris, France).

DOI: 10.1530/endoabs.37.GP.25.01

GP.25.02

Thyroid hormones influence the expression of TNF-related apoptosis-inducing ligand

Stella Bernardi[1,2], Fleur Bossi[1], Fabiola Giudici[1], Paola Secchiero[2], Giorgio Zauli[3] & Bruno Fabris[1]
[1]Department of Medical, Surgical, Health Sciences, University of Trieste, Trieste, Italy; [2]Department of Morphology, Surgery, and Experimental Medicine, LTTA Center, University of Ferrara, Ferrara, Italy; [3]Institute for Maternal and Child Health, IRCCS 'Burlo Garofolo', Trieste, Italy.

Background
There is growing evidence supporting TNF-related apoptosis-inducing ligand (TRAIL) involvement in weight and body composition regulation, which are classically influenced by thyroid hormones. This study aimed at investigating the relationship between thyroid hormones and TRAIL.
Methods
Circulating TRAIL was measured in 40 controls, 40 hyperthyroid, and 25 hypothyroid patients before and after their respective treatments. In the same patients *TRAIL* gene expression was quantified in peripheral blood mononuclear cells. The effect of T_3 and T_4 on TRAIL secretion was evaluated *in vitro*.
Results
TRAIL gene and protein expression significantly increased in hyperthyroid and decreased in hypothyroid patients (vs controls $P < 0.05$). TRAIL gene and protein expression normalized once euthyroidism was restored ($P < 0.05$). There was a significant correlation between TRAIL and both T_3 and T_4 ($P < 0.05$). Moreover, the changes in body weight and BMI that we found once euthyroidism was restored were significantly correlated to the changes in TRAIL ($P < 0.05$). The *in vitro* study showed that T_3 stimulated TRAIL release in a dose-dependent manner.
Conclusion
These findings are consistent with the view that TRAIL might be involved in body weight regulation. In addition, this work sheds light on the possibility that TRAIL might be one of the molecules mediating thyroid hormone peripheral effects.

DOI: 10.1530/endoabs.37.GP.25.02

GP.25.03

Malignancy rate in thyroid nodules with AUS/FLUS cytology in a Cancer Center (Bethesda System for Reporting Thyroid Cytopathology 2009)

Joana Menezes Nunes[1,2], Raquel Martins[2,3], Jacinta Santos[3], Teresa Martins[3], Ana Paula Moniz[4], Olga Ilhéu[4], Paulo Figueiredo[4] & Fernando Rodrigues[3]
[1]Endocrinology, Diabetes and Metabolism Department, Centro Hospitalar S. João, Porto, Portugal; [2]Faculty of Medicine, Oporto University, Porto, Portugal; [3]Endocrinology Department, Instituto Português de Oncologia Francisco Gentil, Coimbra, Portugal; [4]Pathology Department, Instituto Português de Oncologia Francisco Gentil, Coimbra, Portugal.

Introduction
The Bethesda System for Reporting Thyroid Cytopathology is the standard for interpreting fine-needle aspiration (FNA) and created a new diagnostic category (III): 'atypia of undetermined significance/follicular lesion of undetermined significance' (AUS/FLUS). The risk of malignancy for this category has been ascribed of 5–15% but the real malignancy rate remains unclear and plays a key role to define appropriate management.
Objective
To determine malignancy rate in AUS/FLUS cytologies.
Methods
A total of 126 consecutive patients with AUS/FLUS cytology were retrospectively identified. Results of follow-up, repeat biopsy or surgical pathology were evaluated. Data are presented as frequencies. For comparison we performed Student's *t*-test (statistically significance < 0.05).
Results
Among 126 patients, 19.0% (24/126) underwent immediate surgery and 50.0% (63/126) repeated FNA. Of patients immediately submitted to surgery, just one was found to have a papillary microcarcinoma inserted into the index lesion, the remaining suspicious nodules being benign. We found five incidental papillary carcinomas (4 < 1 cm). Repeat FNA cytology was unsatisfactory/non-diagnostic in 22.2% (14/63), benign in 17.5% (11/63), AUS/FLUS in 49.2% (31/63), suspicious for malignancy in 9.5% (6/63), and malignant in 1.6% (1/63). Of nodules with two consecutive AUS/FLUS cytologies that were resected (21/31), 23.8% (5/21) were malignant and in one case the lesion couldn't be determined as benign/malignant. We found no statistical significance regarding nodule size and probability of malignancy of the suspicious nodule (31.7 mm vs 23.0 mm, $P = 0.145$). Overall, 57 patients underwent surgery to remove the index lesion, yielding a malignancy rate of 19.3% (11/57), as one case couldn't be classified by histology. Incidental cancers were found in 21.0% (12/57).
Conclusions
Repeating biopsy allows a significant proportion of AUS/FLUS patients to avoid surgery. In our series, nodules with two AUS/FLUS cytologies harbour a malignancy rate of 23.8%. Incidental papillary carcinomas cancers are frequent (21.0%), in accordance with its high prevalence in general population.

DOI: 10.1530/endoabs.37.GP.25.03

GP.25.04

Evaluation of benign thyroid nodules in a 10-year follow-up

João Silva, Catarina Ivo, Mafalda Marcelino, Hélder Simões, Luís Lopes, Dolores Passos & João Jácome de Castro
Armed Forces University Hospital, Lisbon, Portugal.

Introduction
American Thyroid Association recommends that benign thyroid nodules should be revaluated 6–18 months after initial FNA and in case of stability the follow-up should be 3–5 years. However there isn't any consensus about the periodicity of the follow-up.
Aim
To evaluate the nodules in terms of function, size and malignancy in a 10-year follow-up.

Methods
Retrospective study of 347 patients (543 benign thyroid nodules) followed in consultation. Inclusion criteria: follow-up $\geq$10 years; normal thyroid function; Initial benign FNAC. Evaluation at 5 and 10 years of the following parameters: size, growth (>20% diameter and at least 2 mm in two dimensions), cytology, thyroid function, and therapeutic approach. The variables were analysed by methods of descriptive statistics: frequency tables and contingency for categorical variables and mean, S.D., minimum, and maximum for continuous variables.
Results
We included for analysis 441 nodules of 282 patients, 71% females, mean 56.3$\pm$13.1 years old. The average of nodules size were 18.9$\pm$12.1 mm in the first evaluation. In 5 years 29.45% had increased (mean 9.91$\pm$8.46 mm) and decreased 19.1% (average 8.81$\pm$4.85 mm). In 10 years 31.5% had increased (average 11.53$\pm$7.31 mm) and 15.7% decreased (6.84$\pm$4.83 mm). None of the evaluated nodules turned hyperfunctioning. 17.1% of the evaluated nodules were submitted to surgery, 72% of which for its size (>40 mm or compressive complaints) and the rest by cytological abnormalities. 28% of the nodules revealed to be malignant (4.79% of total).
Conclusions
In this study it was found that about 1/3 of nodules increased in size and 4.79% revealed to be malignant, even with a previous benign cytology. Our results favour a monitoring and a FNAC repetition of the nodules during follow-up, an usual practice in our department.

DOI: 10.1530/endoabs.37.GP.25.04

GP.25.05

Sox9 is expressed in thyroid follicular cells and regulates the expression of thyroid differentiation genes

Arístides López-Márquez, Carlos Carrasco-López & Pilar Santisteban
Instituto de Investigaciones Biomédicas 'Alberto Sols' CSIC–UAM, Madrid, Spain.

The transcription factor Sox9 is a member of the HMG-box-DNA binding family essential for chondrocyte differentiation, sexual determination, and the maintenance of the stem/progenitor cells in several tissues. Furthermore, Sox9 is involved in the development of endoderm-derived-organs. Owing to the endodermic origin of the thyroid, we proposed to study the expression of Sox9 in thyroid follicular cells and its regulation by TSH and TGFβ, two main factors involved in thyroid function. In addition the role of thyroid transcription factors Nkx2-1, FoxE1, and Pax8 was studied. Sox9 mRNA, protein levels and promoter activity were determined by RT-qPCR, western blot, and transient transfection assays after TSH and TGFβ treatment. Forskolin and H89 were used to study the cAMP/PKA pathway. Co-transfections in Hela cells were performed to elucidate the role of the different transcription factors in the regulation of Sox9 as well as its role over other thyroid specific genes. We showed that Sox9 is expressed in thyroid cells and TSH induced the mRNA, protein levels and promoter activity, while TGFβ inhibited the TSH induction. The TSH effect takes place through cAMP/PKA pathway as forskolin mimics its effects and the PKA inhibitor H89 inhibited it. The *in silico* analysis of Sox9 promoter reveals the presence of CRE, Smad and thyroid transcription factors binding sites. The results obtained have demonstrated that Sox9 promoter is activated by Pax8 and CREB and inhibited by FoxE1. Interestingly, Sox9 activates FoxE1 promoter while inhibited Nkx2-1 and Pax8 ones. These results demonstrate the involvement of Sox9 in the physiology of the thyroid, something hitherto unknown. In addition our results open a new field to study the role of Sox9 in the development and differentiation of the thyroid gland.
Disclosure
SAF2013-44709R from Ministerio de Economia y Competitividad S2011/BMD-2328-Tironet from the Comunidad de Madrid.

DOI: 10.1530/endoabs.37.GP.25.05

GP.25.06

Clinical outcome of thyroid nodules characterised as atypia of undetermined significance or follicular lesion of undetermined significance (The Bethesda System for Reporting Thyroid Cytopathology) after fine-needle aspiration

Fernando García[1], Mariana Tomé[2], Guillermo Martínez de Pinillos[1], Eyveé Arturo Cuéllar[1], Mariola Méndez[1], Juan Manuel García de Quirós[1], Ignacio Fernández Peña[1], Ignacio Fernández López[1], Juana Hidalgo[1], Margarita Rivas[1], Santiago Durán[1] & María Victoria Cózar[1]
[1]Hospital de Valme, Seville, Spain; [2]Hospital Punta Europa, Cádiz, Spain.

Introduction
'Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance' category is established by The Bethesda System for Reporting Thyroid Cytopathology because of the necessity to report those thyroid fine-needle aspiration (FNA) results that are not easily classified into the benign, suspicious or malignant categories. In most cases, a repeated FNA results in a more definitive interpretation. Estimated risk of malignancy for an AUS nodule is 5–15%.
Description of methods
A restrospective study was conducted in which those patients with a result of AUS after thyroid FNA between 2010 and 2013 were included. The following variables were considered: proportion of repeated FNA and average time of delay; consistency between repeated and initial FNA; therapeutical management and malignancy incidence rate.
Results
We studied 59 patients (94.9% females, mean age 48.3$\pm$14.3 years). FNA was repeated in 76.3% of patients with an average delay of 195.5$\pm$125.4 days between both FNA. We achieved the following interpretations: benign 55.6%; persistent AUS 17.8%; follicular neoplasm or suspicious of folicular neoplasm 17.8%; and suspicious for malignancy 8.9%. Thyroidectomy was performed in 55.2% of all patients (40.6% without repeating FNA and 59.4% after repeating FNA). In all cases lobectomy was the selected procedure. The incidence of malignancy was 10.2% of the total sample (18.2% of patients who underwent surgery).
Conclusion
Repeating FNA in patients with a result of 'atypia of undetermined significance/folicular lesion of undetermined significance' may contribute to clarify the diagnosis in a large number of cases, helping in the selection of patients who should undergo surgery or alternatively should be observed clinically. The incidence of malignancy detected in our series is consistent with the incidence expected by The Bethesda System.

DOI: 10.1530/endoabs.37.GP.25.06

GP.25.07

Malignancy risk stratification of thyroid nodules by TIRADS; correlation with cytological results

Antonio J Martínez, Virginia Hernando, Clara García, Alberto Torres & Tomás Martín
Virgen Macarena Hospital, Seville, Spain.

Introduction
Knowing that only in 5–15% of FNABs the pathological analysis shows malignancy, enhance diagnostic accuracy is needed. The use of the TIRADS score and a revised version proposed by the British Thyroid Association (BTA) intend to determine if a FNAB should be performed or not in the evaluation of nodular goitre.
Objective
To determine whether an adequate correlation is present between the risk category assigned to the nodules studied under TIRADS/BTA system and cytological results.
Material and methods
To assess the potential of the TIRADS/BTA systems and the degree of concordance with the results derived from FNAB, we designed a retrospective, observational study including 230 patients who underwent thyroid ultrasonography and FNAB. Nodules were classified following the BTA score as benign (U2), probably benign (U3), and suspicious/probably malignant (U4+5). FNAB samples were informed according to the Bethesda classification. Statistical analysis was assessed using the SPSS Statistical Suite (ver 21.0).
Results
Total sample n=230 (valid pairs, n=204); 71.3% females, mean age 59.2$\pm$5.6 years. U2 nodules were 76%; in one case (0.7%) the pathological analysis was consistent with malignancy/suspicious for malignancy while the rest of them (99.3%) were informed as benign. U3 nodules comprised 18 nodules, from which 55% had a benign pathological diagnosis, 16.66% probably benign, and 27.77% malignant or suspicious for malignancy. The high-risk group (U4+5) included n=31 (15.1%) nodules: FNAB results showed a malignant/suspicious for malignancy diagnosis in 80.6%, in 12.9% benign, and in 6.4% probably benign. TIRADS score sensitivity was 75% (95% CI: 57.79–87.85%); specificity was 97.62% (95% CI: 94.01–99.33%), with a positive predictive value of 87.1% and a negative predictive value of 94.8%. Cohen's κ coefficient was 0.69 (P<0.001).
Conclusions
The TIRADS/BTA risk scores have proven to be a useful tool to assess thyroid nodules and the need for FNAB, enhancing diagnostic accuracy and resource allocation.

DOI: 10.1530/endoabs.37.GP.25.07

Thyroid - hypothyroidism

GP.26.01

Quality of life in primary hypothyroidism after long-term levothyroxine replacement

Marina Djurovic[1], Alberto Pereira[2], Olga Vasovic[3], Zvezdana Jemuovic[1], Dragan Pavlovic[4], Milan Petakov[1], Biljana Salak[5] & Svetozar Damjanovic[1]
[1]Clinic for Endocrinology, Diabetes and Diseases of Metabolism, Clinical Centre of Serbia, University of Belgrade, Belgrade, Serbia; [2]Department of Endocrinology and Metabolic Diseases, Leiden University Medical Center, Leiden, The Netherlands; [3]Institute for Gerontology and Palliative Care, Belgrade, Serbia; [4]Faculty of Philosophy, University of Belgrade, Belgrade, Serbia; [5]Institute of Neurology, Clinical Centre of Serbia, University of Belgrade, Belgrade, Serbia.

Introduction
There is an increasing awareness for intrinsic imperfections of endocrine replacement therapy affecting general well-being in the long-term. For thyroid hormone, many factors affect the variable responses to hormone replacement, like common genetic variations in deiodinase and thyroid hormone transport proteins, and the inability to provide adequate individual combined T_4 and T_3 therapy. Despite levothyroxine (L-T_4) replacement in primary hypothyroidism and restoration of biochemical euthyroidism, many patients have persistent complaints that have anecdotally been associated to high levels of antibodies against TPO (anti-TPO).
Aim of the study
i) To assess quality of life (QoL) in patients with Hashimoto's thyroiditis (HT) on adequate L-T_4 replacement and ii) to explore potential associations with serum TSH and anti-TPO.
Design
Cross-sectional, case–control study.
Patients and controls
One hundred and twenty patients on long-term L-T_4 replacement for HT (mean age 54.0 ± 14.0 years, range 21–75 years) and 60 euthyroid control subjects (aged 53.1 ± 12.4), matched for age, gender, and educational level.
Methods
Evaluation of FT_4, TSH, and anti-TPO concentrations, and of QoL as measured with the Short Form-36 Health Survey (SF-36) for mental health and vitality in both patients and controls. Patients and controls were subdivided into two age groups: 20–49 years (GR1) and 50–75 years (GR2), with a mean duration of L-T_4 replacement of 3.95 and 9.27 years respectively.
Results
FT_4 and FT_3 levels were not different between patients and controls, but TSH was slightly higher in Hashimoto patients (GR1 3.64 ± 2.74 vs 1.93 ± 1.10, $P<0.05$ and GR2 3.93 ± 2.84 vs 1.91 ± 0.90, $P<0.05$). SF-36 scores in the patients were significantly lower for both age groups compared with controls (patients vs controls): dimension A–physical health; GR1: 70.18 ± 15.74 vs 76.54 ± 13.71, $P<0.05$; GR2: 55.84 ± 20.2 vs 75.1 ± 121.0, $P<0.01$; SF-36 score GR1: 69.8 ± 16.4 vs 76.4 ± 14.1, $P<0.05$; GR2: 57.6 ± 21.1 vs 73.7 ± 14.2, $P<0.05$. In addition, in both groups anti-TPO levels, but not TSH, were associated with SF-36 scores subscale2 $r=-0.208$, $P=0.029$; subcale3 (body pain) $r=-0.268$, $P=0.005$; subcale4 (general health) $r=-0.198$, $P=0.038$; dimension A $r=-0.224$, $P=0.019$; and SF-36 score $r=-0.191$, $P=0.046$.
Conclusion
Patients on long-term L-T_4 replacement for HT have impaired QoL that is associated with higher anti-TPO levels.

DOI: 10.1530/endoabs.37.GP.26.01

GP.26.02

High serum IgG4 concentrations in patients with Hashimoto's thyroiditis

Anna Poplawska-Kita, Maria Kosciuszko-Zdrodowska, Katarzyna Siewko, Beata Telejko, Justyna Hryniewicka, Robert Milewski, Małgorzata Szelachowska & Maria Gorska
Medical University of Bialystok, Bialystok, Poland.

Purpose
Recent reports strongly suggest that at least some cases of Hashimoto's thyroiditis (HT) may be closely associated with IgG4-related disease. In the present study we aimed to find out, whether the measurement of serum IgG4 allows for an identification of distinct types of HT, with different clinical, sonographic and serologic characteristics.
Methods
The group studied consisted of 53 patients with HT and 28 healthy individuals. All the participants underwent thyroid ultrasonography and body composition analysis. Serum concentrations of IgG4, TSH, anti-peroxidase antibodies (TPOAb), anti-TSH receptor antibodies, TNFα, TGF-β1, Fas ligand, TRAIL, and chemokines: CXCL9, CXCL11, and CXCL10 were also measured by commercial ELISA or RIA.
Results
The group with IgG4 level >135 IU/ml accounted for 32.5% of the patients. The percentage of male patients was 7.5% in the subgroup with normal IgG4 and 18.2% in the subgroup with high IgG4 concentration. The signs of fibrosis were present in 27.0% of the high-IgG4 patients and in 9.1% of the normal-IgG4 group. The patients with elevated IgG4 required higher doses of L-thyroxine, had significantly lower level of TPOAb ($P=0.02$) than the non-IgG4-HT individuals, and higher TNFα level in comparison with the controls ($P=0.01$); whereas the concentrations of other cytokines/chemokines and apoptotic markers did not differ between the groups studied.
Conclusions
Our results suggest that the measurement of serum IgG4 allows for an early identification of patients more rapidly progressing and destructive form of HT, who require higher doses of L-thyroxine. A relatively low TPOAb level and the absence of co-existing autoimmune diseases may suggest a distinct pathomechanism of this type of thyroiditis.
Disclosure
The study was supported by grant number 123-50-723L from the Medical University of Bialystok, Poland.

DOI: 10.1530/endoabs.37.GP.26.02

GP.26.03

Adverse metabolic correlations relate to free T_3 levels in subclinical hypothyroidism; common FOXE1 polymorphisms associate with blood pressure

Anna de Lloyd[1], Ilaria Muller[1], Alan Dodd[2], Ameen Bakhsh[1], Hilary Durrant[2], Lei Zhang[1], Carol Evans[2], Aled Rees[1] & Marian Ludgate[1]
[1]Thyroid Research Group, IMEM, Cardiff University, Cardiff, UK; [2]Department of Medical Biochemistry and Immunology, University Hospital of Wales, Wales, UK.

Introduction
The effects of mild subclinical hypothyroidism (SH; TSH <10 mU/l) on metabolic outcomes are unclear. This may relate to differences in aetiology, including thyroid autoimmunity or genetic factors such as TSH-receptor mutations (TSHR-M) and FOXE1 polyalanine tract length (FOXE1–PTL) polymorphisms, which are associated with altered thyroid function. We hypothesised that the metabolic manifestations of SH may depend upon its aetiology.
Aims
i) To establish whether free T_4, free T_3, or TSH associate with metabolic parameters and blood pressure (BP) in SH. ii) To investigate whether SH aetiology has a differential effect on metabolic parameters and BP.
Methods
A total of 208 adults with primary untreated SH (TSH ≥ 5 mU/l) were recruited and underwent a medical/lifestyle history, resting BP and BMI measurement, genetic evaluation (for TSHR-M and FOXE1–PTL status), thyroid function, anti-TPO antibody measurement, and metabolic assessments (HOMA-IR, full lipid profile). Associations were examined using stepwise multivariate regression analyses.
Results
TSH showed a small positive association with free T_3 (R $+0.6$, $P=0.01$) and a negative association with free T_4 (R -1.1, $P<0.001$) but no association with metabolic factors or BP. Free T_3 showed a positive association with BP (systolic R $+10$, $P<0.001$ and diastolic R $+3$, $P=0.02$) and HOMA-IR (R $+1.3$, $P=0.009$). No significant metabolic associations were found for TSHR-M or TPO antibody positivity. The 14/14 FOXE1–PTL (60% of cohort) was positively associated with free T_3 compared to other genotypes (R $+0.2$, $P=0.007$) and negatively associated with BP (systolic R -6, $P=0.006$ and diastolic R -4, $P=0.01$).
Conclusions
Free T_3 correlated positively with BP and HOMA-IR in this cohort, irrespective of SH aetiology. An unexpected association between FOXE1–PTL polymorphisms and BP was revealed.
Disclosure
Society for Endocrinology grant.

DOI: 10.1530/endoabs.37.GP.26.03

GP.26.04

Nkx2.5 gene mutations are not associated with congenital heart defects in children with thyroid dysgenesis

Helton Estrela Ramos[1,2], Taise Lima de Oliveira Cerqueira[2], Yane Rocha Ramos[1], Paula Leite[3], Jailciele Santos[1], Daniel San Martin[1], Anabel Goes Costa[3], Vladimir Fernandes[4], Giorgia Strappa[1], Mariana Souza de Jesus[1], Tatiana Amorim[5] & Ana Marice Ladeia[3]
[1]Universidade Federal da Bahia, Salvador, Bahia, Brazil; [2]Centro de Pesquisa Gonçalo Moniz – FIOCRUZ, Salvador, Bahia, Brazil; [3]Escola Bahiana de Medicina e Saúde Pública, Salvador, Bahia, Brazil; [4]Diagnoson – Grupo Fleury, Salvador, Bahia, Brazil; [5]Associação de Pais e Amigos dos Excepcionais – APAE, Salvador, Bahia, Brazil.

Context
Several specific transcriptional factors, in view of their important role in thyroid organogenesis and thyroid specific gene expression, would be strong candidate genes for the etiology of TD. The homeobox transcription factor *NKX2.5* was thought to be only required for the organogenesis of the heart tube. However, *NKX2.5*$^{-/-}$ embryos also exhibited a smaller outgrowing thyroid bud. Indeed, several loss of function mutations in *NKX2.5* have been described in patients with congenital heart disease (CHD), and an Italian study has identified three mutations in patients with TD.
Objectives
To search for genetic alteration in *NKX2.5* gene in patients presenting both TD/CHD and isolated TD.
Methods
Among 1051 neonates screened between 2001 and 2013, 851 children were identified with CH. Individual phenotypes were analyzed in 86 children with TD using thyroid function tests (TT_4 and TSH), scintigraphy and ultrasound as diagnostic tools. Seven patients had CHD and TD. DNA was extracted from whole blood and *NKX2.5* gene coding region was amplified by PCR and sequenced.
Results
CHD were found in 8.1% of patients with TD investigated. The mutation screening revealed two known polymorphisms in 48 patients with isolated TD or TD associated with CHD. None of them are predicted to result in codon change in conserved domain (p.Glu21; p.Gln181).
Conclusion
NKX2.5 mutations were not found in patients having TD or TD associated with CHD. *NKX2.5* gene might not be a strong candidate gene for mutation screening in population based studies. It would be of interest to attempt to identify additional NKX2.5 downstream target genes and upstream signaling pathways for a more complete knowledge of the function of this homeobox protein during thyroid migration and morphogenesis.
Disclosure
Fundação de Amparo a Pesquisa do Estado da Bahia.
DOI: 10.1530/endoabs.37.GP.26.04

GP.26.05

Oral liquid thyroxine assumed at breakfast: preliminary results of the TICO study

Ilenia Pirola, Annamaria Formenti, Linda Daffini, Alessandra Cristiano, Elena Gandossi, Floriana Pini & Carlo Cappelli
Endocrine and Metabolic Unit, Department of Medical and Surgical Sciences, University of Brescia, Brescia, Italy.

Many conditions may interfere with intestinal absorption of levothyroxine (L-T_4). In addition, it has been demonstrated a failure in the normalisation of TSH values in patients consuming L-T_4 tablets with coffee or with water followed by coffee taken shortly afterwards. Recent studies showed that oral liquid L-T_4 could remove the problem of L-T_4 malabsorption by coffee and food observed with traditional tablets formulations. To evaluate the efficacy of oral liquid T_4 assumed at breakfast, we conducted the TICO study: a double-blind, placebo-controlled trial, designed to enrolled 80–100 hypothyroid patients, aged from 18 to 75 years who have to start replacement therapy. All the patients were given two identical and indistinguishable vials (labelled A and B), one containing in a single dose of the oral solution and the other a placebo; one had to be assumed half an hour before breakfast and the other one during their usual breakfast. After 40 days of treatment, all the patients were submitted to TSH, fT_4, and fT_3 evaluation to ensure euthyroidism values had been reached. All the patients then had to switch the order in which the vial contents were ingested. After 40 days, TSH, fT_4, and fT_3 values were re-tested. At this time 72 patients (54/18 females/males, mean age 48.8±5.7 years old) completed the study. The mean dose of L-T_4 was 64.71±30.17 μg/day. At the end of the study no differences to TSH serum (2.84±1.91 mIU/l vs 2.62±1.76 mIU/l, $P=0.470$), fT_4 (10.57±1.32 pg/ml vs 10.44±1.24 pg/ml, $P=0.546$), and fT_3 (2.75±0.36 pg/ml vs 2.85±0.28 pg/ml, $P=0.193$) were observed among the patients whether assuming vials A or vials B at breakfast. In conclusion, we have clearly demonstrated that liquid L-T_4 can be taken at breakfast, facilitating compliance to L-T_4 replacement therapy. Finally, the oral solution L-T_4 could be suitable for patients who cannot swallow the solid formulations.

DOI: 10.1530/endoabs.37.GP.26.05

GP.26.06

Analysis of hypothyroidism in patients admitted to internal medicine wards in Spain 2005–2012

Rona Penso[1], Alejandra Duran[1], Teresa Ruiz Gracia[1], Irene Crespo[1], Ana Ortola[1], Paz De Miguel[1], Manuel Mendez[1], Karla Nuñez[1], Judith Lopez[2] & Javier Marco[1]
[1]Hospital Clinico San Carlos, Madrid, Spain; [2]Hospital Universitario de Canarias, San Cristobal de la Laguna, Spain.

Introduction
Hypothyroidism (hT) is a very common disease that can affect inpatients prognosis. We analysed the clinical profile of patients with hT admitted to Internal Medicine using a large clinical-administrative database.
Methods
A descriptive analysis based on the minimum-data-set database of the Spanish National health System of patients who were discharged from the services of Internal Medicine with the diagnoses of hT during 2005–2012 was performed.
Results
A total of 3 984 533 patients admitted to Internal Medicine were included, identifying 141 616 cases of hT (3.6%). From the population 75.8% were women, average age in hT patients was 74.34 (S.D.: 14.30). Overall mortality in hT group was 7.6% vs 10% in nonhT (nhT). The 14.3% of the patients hT were readmitted, whereas in the whole population the 13.3% did it. The average hospital stay was 9.73 (S.D.: 10.04) days. The comorbidities associated to hT were as follows: connective tissue disease (2.2% in hT vs 1.1% in nonhT), diabetes mellitus (32.5% vs 27.5% respectively), hypertension (42.1% vs 36.9% respectively), hypercholesterolemia (23.4% vs 16.2% respectively), obesity (12.8% vs 7.5% respectively), anemia (21.9% vs 16.1% respectively), and chronic renal impairment (15.9% vs 11.5% respectively). In the multivariable analysis hT was associated to a lower mortality rate OR 0.71 (95% CI 0.70–0.73; $P<0.05$). In the adjusted analysis by age (95% CI 1.052–1.053; $P<0.05$) and by comorbidities Charlson index OR 1.246 (95% CI 1.245–1.248; $P<0.05$).
Conclusion
Hypothyroidism was associated with cardiovascular risk factors as well as other comorbidities (obesity, anemia, kidney failure, and connective tissue pathologies). Some authors suggest that the increase in TSH levels could have a protective effect during admission. However, surprisingly in the hT group there was lower mortality rate. Further studies are needed to confirm this results and determinate other involved factors.

DOI: 10.1530/endoabs.37.GP.26.06

GP.26.07

Cardiovascular risk factors in autoimmune thyroiditis and subclinical hypothyroidism

Celestino Neves[1], César Esteves[1], João Sérgio Neves[1], Oksana Sokhatska[2], Miguel Pereira[1], Carmo Palmares[2], Camila Dias[3], Davide Carvalho[1], Luís Delgado[2] & José Luís Medina[1]
[1]Endocrinology Service, Faculty of Medicine, São João Hospital, University of Porto, Porto, Portugal; [2]Immunology Department, Faculty of Medicine, São João Hospital, University of Porto, Porto, Portugal; [3]Department of Biostatistics and Medical Informatics, Faculty of Medicine, São João Hospital, University of Porto, Porto, Portugal.

Introduction
Subclinical hypothyroidism appears to be related with an increased risk of cardiovascular disease. It was our objective to evaluate the relationship between autoimmune thyroiditis, subclinical hypothyroidism, and cardiovascular risk factors.
Methods
We evaluated thyroid function tests, autoimmunity, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, ApoA1, ApoB, Lp(a), homocysteine, high sensibility CPR, folic acid, vitamin B12, HOMA-IR, HOMA-β, QUICKI,

HISI, WBISI, and IGI in 186 subjects with autoimmune thyroiditis and in euthyroid state and in 69 subjects with autoimmune thyroiditis and subclinical hypothyroidism. Statistical analysis was performed with Mann–Whitney *U* test, logistic regression, and Spearman correlations. In our study group, 94% of patients were females. The median age was higher in the euthyroid group (49 years vs 42 years; $P=0.03$). The results were adjusted for age and BMI and are expressed by median ± percentiles 25 and 75. Statistical significance was considered for a bilateral value of $P<0.05$.

Results

Patients with higher levels of total cholesterol (OR = 1.008; $P=0.03$), CPR (OR = 1.684; $P=0.04$), or anti-thyroglobulin antibodies (OR = 1.002; $P=0.02$) have an increased likelihood of having subclinical hypothyroidism. In the total group of patients, we observed positive correlations between TSH and CPR ($r=0.132$; $P=0.043$), between TSH and HOMA-IR ($r=0.158$; $P=0.029$), between free T_3 and HDL-cholesterol ($r=0.16$; $P<0.01$), and between free T_4 and IGI ($r=0.22$; $P<0.01$). TSH levels correlated negatively with QUICKI ($r=-0.16$; $P=0.02$), HISI ($r=-0.16$; $P=0.03$) and WBISI ($r=-0.16$; $P=0.02$) and free T_4 levels with WBISI ($r=-0.18$; $P=0.01$). In the group with subclinical hypothyroidism, we found negative correlations between free T_3 and homocysteine ($r=-0.36$; $P=0.01$) and between free T_4 levels and anti-TPO antibodies ($r=-0.28$; $P=0.02$).

Conclusion

The interrelations between thyroid function, lipid profile, CPR, and insulin resistance demonstrate an increase of cardiovascular risk in subclinical hypothyroidism due to autoimmune thyroiditis.

DOI: 10.1530/endoabs.37.GP.26.07

GP.26.08

Prevalence and clinical associations of calcium-sensing receptor and NALP5 autoantibodies in patients with autoimmune polyendocrine syndrome type 1

Mahmoud Habibullah[1], Nicolas Kluger[2], Annamari Ranki[2], Harpreet Sandhu[1], Kai Krohn[3], Anthony Weetman[1] & Helen Kemp[1]
[1]University of Sheffield, Sheffield, UK; [2]University of Helsinki, Helsinki, Finland; [3]Helsinki University Central Hospital, Helsinki, Finland.

Rationale and hypothesis

Autoimmune polyendocrine syndrome type 1 (APS1) is a rare autosomal recessive disease which is characterised by chronic mucocutaneous candidiasis and multiple autoimmune endocrinopathies and results from mutations in the autoimmune regulator (*AIRE*) gene. Approximately 80% of APS1 patients present with hypoparathyroidism which is suggested to result from aberrant immune responses against the parathyroid gland. As patients typically display organ-specific autoantibodies which correlate with a particular clinical manifestation, there has been much research to identify a parathyroid-specific autoantibody target. Previous studies have identified the parathyroid-expressed calcium-sensing receptor (CaSR) and NALP5 as autoantigens in APS1. However, it is unclear if autoantibodies against CaSR or NALP5 are a specific or sensitive marker for APS1-associated hypoparathyroidism.

Methodology

A case–control study including 44 APS1 patients and 38 healthy control subjects. Methods included ELISA; radioligand binding assays; immunoprecipitation assays; DNA sequencing; and statistical analysis.

Findings

CaSR and NALP5 autoantibodies were detected in 16/44 (36%) and 13/44 (30%) of APS1 patients, respectively, but not in healthy control subjects. No statistically significant association was found between the presence of CaSR or NALP5 autoantibodies and hypoparathyroidism ($P>0.05$). The detection of CaSR and NALP5 autoantibodies had specificities of 83 and 50%, and sensitivities of 39 and 26%, respectively, for the diagnosis of hypoparathyroidism. There were no significant associations between the presence of CaSR or NALP5 autoantibodies and either sex, age, or age at disease presentation (P values were >0.05). However, a significant association between a shorter APS1 duration (<10 years) and positivity for CaSR autoantibodies was noted ($P=0.019$). This was not the case for NALP5 autoantibodies.

Conclusions

Since CaSR and NALP5 autoantibodies are not specific or sensitive markers for hypoparathyroidism in APS1, further investigations are required to identify a useful diagnostic marker for this clinical manifestation in APS1.

Disclosure

The research is funded by University of Jazan, Saudi Arabia.

DOI: 10.1530/endoabs.37.GP.26.08

GP.26.09

No effect of Thr92Ala DIO2 polymorphisms on thyroid parameters, health-related quality of life, and cognitive functioning

Bruce H R Wolffenbuttel, Hannah C M van Loon, Martin F Elderson, Jana V van Vliet-Ostaptchouk, Hanneke J C M Wouters, Anneke Muller Kobold, Thera P Links, Sandra N Slagter & Melanie M van der Klauw
University of Groningen, Univ Med Ctr Groningen, Groningen, The Netherlands.

Introduction

The Thr92Ala polymorphism of deiodinase 2 (DIO2) is associated with increased expression in the brain of genes associated with oxidative stress, and may predict favourable response to combination thyroxine (L-T_4) plus triiodothyronine (T_3) therapy. We examined whether the Thr92Ala polymorphism (rs225014) was associated with differences in thyroid hormone parameters, health-related quality of life (HR-QOL) and cognitive functioning in a large population-based study.

Methods

In 4223 participants from the LifeLines Cohort Study (141 using L-T_4) TSH, free thyroxine (FT_4), and free T_3 (FT_3) levels were measured. HR-QOL was assessed with the Short Form-36 questionnaire. The Ruff figural fluency test (RFFT) was used as a sensitive cognitive test. Linear regression with an additive model was used to analyse association between the Thr92Ala genotypes and phenotypes of interest.

Results

Mean (± S.D.) age was 56 ± 10 years and BMI 27.3 ± 4.4 kg/m^2 in the L-T_4 users vs 51 ± 11 years and 26.4 ± 4.1 kg/m^2 in non-L-T_4 users; 3847 subjects had normal TSH (0.4–4.5 mU/l), and 90% of L-T_4 users were females. The rarer CC genotype (Thr92Ala-D2) of the rs225014 polymorphism in DIO2 was present in 10.2% of the total study population. In non-L-T_4 users, the Thr92Ala-D2 polymorphism was not associated with differences in TSH, FT_4, FT_3, and the FT_3/FT_4-ratio, and there were no differences in any of the eight HR-QOL domains or the RFFT score. L-T_4 users had higher FT_4, lower FT_3 and lower FT_3/FT_4-ratio, lower scores on the HR-QOL domains physical functioning, general health and vitality (all $P<0.001$) and lower RFFT scores ($P=0.004$). Also, their thyroid hormone parameters, HR-QOL and cognitive functioning were not influenced by the Thr92Ala genotype.

Conclusion

The Thr92Ala polymorphism of DIO2 was not associated with thyroid parameters, HR-QOL and cognitive functioning in the general population and subjects with hypothyroidism.

Disclosure

This work was supported by NCHA, Netherlands Consortium for Healthy Ageing, Bio-SHaRE-EU, Biobank Standardisation and Harmonisation for research excellence in the European Union. Bioresource research impact factor BRIF4568.

DOI: 10.1530/endoabs.37.GP.26.09

GP.26.10

HLA-DR in Hashimoto's thyroiditis

Agata Jabrocka-Hybel[1,2], Anna Skalniak[1,2], Jakub Piętkowski[1,2], Renata Turek-Jabrocka[1,2], Palina Vyhouskaya[1], Adrian Tsang[3], Katarzyna Lizis-Kolus[4], Grzegorz Sokołowski[2], Dorota Pach[1,2] & Alicja Hubalewska-Dydejczyk[1,2]
[1]Jagiellonian University Medical College, Krakow, Poland; [2]University Hospital in Krakow, Krakow, Poland; [3]University of Ottawa, Ottawa, Ontario, Canada; [4]Swietokrzyskie Oncology Centre, Kielce, Poland.

Background

The human leukocyte antigen (HLA) cluster is a genetic region that has been associated with multiple autoimmune disorders, also with autoimmune thyroid diseases. Plenty attempts to establish the significance of class II HLA-DR in Hashimoto's thyroiditis (HT) development were undertaken in the past; however, reports are rather divergent. This might be caused by different criteria used to diagnose HT. There is however an alternative hypothesis, according to which a specific amino acid signature in the binding cleft, found among different types, might be more important in triggering susceptibility to HT than the type itself.

Aim

The presented study tests the hypothesis of whether and how HLA-DR can alter HT risk.

Materials and methods

Five hundred unrelated Hashimoto cases and healthy controls were studied. Including criteria for HT were in accordance with current recommendations (positive auto-antibodies, hypothyroidism, characteristic ultrasound). We sequenced the binding cleft-encoding exon of *HLA-DRB1* in all participants. For differences of allele frequencies between groups the χ^2 test was implemented.

Stepwise logistic regression analysis was performed for testing the importance of amino acid signatures of the binding cleft.
Results and conclusions
We show results for HLA-DR of a big project on the genetics of HT. We found that, indeed, the amino acid signature of the binding cleft, encompassing positions 26, 30, 70, 71, and 74, might be important for the development of the disease, but our results let us also conclude that this model would explain only about 5% of the susceptibility to HT. The results for HLA-DR may also differ when additional genetic and environmental factors are considered simultaneously. It therefore seems reasonable to include this genetic region into analyses encompassing multiple genes as well as non-genetic factors. This will be the next step of our ongoing project.
Disclosure
This work was supported by the Polish National Science Centre – grant number DEC-2011/01/B/NZ5/00337 and by the Polish Ministry of Science and Higher Education – grant number K/ZDS/003694.
DOI: 10.1530/endoabs.37.GP.26.10

Thyroid - hyperthyroidism and treatment

GP.27.01

The effect of TSH suppression therapy on the cortical bone geometry in the patients with differentiated thyroid cancer

Jae Hoon Moon[1], Hoon Sung Choi[3], Chan Hyun Jung[2], Kyung Young Kim[2], Young Joo Park[2], Do Joon Park[2] & Kyong Yeun Kim[1]
[1]Seoul National University Bounding Hospital, Seongnam, Republic of Korea; [2]Seoul National University Hospital, Seoul, Republic of Korea; [3]Kangwon National University Hospital, Kangwon-do, Republic of Korea.

Background
TSH suppression therapy has been associated with hip and vertebral fracture. However, the relationship between TSH suppression and bone mineral density (BMD) remains controversial. The aim of this study was to evaluate the effect of TSH suppression therapy on cortical bone geometry in differentiated thyroid cancer (DTC) patients.
Methods
This study included 122 subjects (19 men, 27 premenopausal women, and 75 postmenopausal women) who have been on TSH-suppressive doses of levothyroxine after thyroidectomy due to DTC during at least 3 years. Patients were matched with 366 healthy controls. Dual-energy X-ray absorptiometry at the hip and lumbar spine was performed and geometry of hip was analysed.
Results
The mean TSH level was 0.23 ± 0.44 μIU/ml and the proportion of calcium/vitamin D supplement was 51.6% in 122 subjects. TSH suppression therapy did not impair the BMD of patients compared with controls. In addition, cortical bone geometry including cortical width of femur neck (5.5 ± 1.9 vs 5.4 ± 1.1, $P=0.903$ in men, 5.9 ± 1.1 vs 5.0 ± 0.6, $P=0.079$ in premenopausal women, and 5.0 ± 0.9 vs 5.1 ± 0.7, $P=0.563$ in postmenopausal women) and buckling ratio (4.0 ± 2.1 vs 4.0 ± 1.4 in male, 3.0 ± 0.8 vs 3.4 ± 0.3 in premenopausal women, and 3.6 ± 0.7 vs 3.5 ± 0.6 in postmenopausal women) showed no significant difference in patients compared to healthy controls.
Conclusions
There was little evidence of adverse effect of TSH suppression on cortical bone geometry in DTC patients.
DOI: 10.1530/endoabs.37.GP.27.01

GP.27.02

MIVAT vs traditional thyroidectomy: a 5-year follow up in 284 cases

Elisa Bertocchi, Paolo Del Rio, Lorenzo Viani, Elena Bonati & Mario Sianesi
General Surgery and Organ Transplantation, University Hospital of Parma, Parma, Italy.

Introduction
Minimally invasive video-assisted thyroidectomy (MIVAT) was introduced for the treatment of selected patients. Our experience from 2005 indicates that outcome of surgery in differentiated thyroid cancer (DTC) is comparable in patients treated with MIVAT vs conventional thyroidectomy; minimally invasive technique is characterized by a better postoperative discomfort.
Material and methods
In this prospective study from July 2005 to December 2009, 284 patients with cytological negative node underwent either MIVAT ($n=102$) or conventional thyroidectomy ($n=182$). The following criteria for MIVAT were applied: thyroid volume, nodule size, and pathological criteria. We have collected age, nodule mean size, operative time, serum calcium level pre and post surgery. In follow-up these data were recorded: cumulative dose of radio-active iodine (RAI) and serum thyroglobulin (Tg) at 5 years.
Results
The clinical parameters of the MIVAT and conventional thyroidectomy groups were comparable except for age (mean 44.8 ± 9.9 years vs 52.3 ± 14.1 years, $P=0.03$) and operative time (mean 63 ± 23.5 min vs 54 ± 15.4 min, $P=0.02$); the mean tumour size was similar between groups (1.3 ± 0.6 cm vs 1.6 ± 0.8 cm, $P=0.15$). Surgical morbidity was similar in both groups. Median follow-up was 5 years. RAI dose (mean 73 ± 36 mCu vs 97 ± 45 mCu, $P=0.33$) and serum Tg at 5 years (mean 0.4 ± 0.1 years vs 0.4 ± 0.2 years, $P=0.3$) were not significantly different between the minimally invasive and the conventional thyroidectomy groups.
Conclusion
MIVAT can be safely utilised in patients with DTC providing early oncological outcome comparable to conventional thyroidectomy. Patients treated with minimally invasive surgery showed an improvement of postoperative pain and cosmetic result.
DOI: 10.1530/endoabs.37.GP.27.02

GP.27.03

Clinical and biochemical factors affecting prognosis of disease persistence in micro papillary thyroid carcinomas

Katerina Saltiki, Michael Apostolakis, Sophia Kouki, Loukia Spanou, Anastasia Athanasiadou, Evangelia Zapanti & Maria Alevizaki
Endocrine Unit, Department of Medical Therapeutics, Alexandra Hospital, Athens, Greece.

Introduction
In recent years, micro papillary thyroid carcinomas (mPTCs; ≤ 1.0 cm) are increasingly diagnosed. Although clinical course is usually favourable, disease persistence may occur and multiple treatments needed. We examined factors that could be predictors of clinical behaviour and disease persistence.
Patients and methods
478 mPTC patients (78.9% females) followed-up for 0.6–10 years were classified according to tumour size in group 1: 0.1–0.2 ($n=85$), group 2: 0.3–0.4 ($n=81$), group 3: 0.5–0.6 ($n=96$), group 4: 0.7–0.8 ($n=79$), and group 5: 0.9–1.0 cm ($n=137$).
Results
Median age at diagnosis, sex and histological type did not differ between subgroups. Capsular and lymph node invasion as well as soft tissue involvement was more frequent with increasing tumor size ($P<0.001$). Multifocality and distant metastasis at diagnosis was similar. Patients with mPTCs ≥ 0.7 cm (groups 4 and 5) underwent more frequently lymph node dissection ($P=0.009$) as well as ablation with ^{131}I ($P<0.001$). In those who underwent thyroid ablation, disease remission during the 12-month Tg-stimulation (Tg ≤ 1.0 ng/ml) was less frequent in group 5 (group 1: 85.7%, group 2: 88.2%, group 3: 92.7%, group 4: 85.4%, and group 5: 69.1%, $P=0.007$). However, after multiple treatments (>1 surgeries and/or repeated ^{131}I administration) the disease outcome did not differ significantly. The 10-year probability of lack of progression of disease did not differ between groups (100% vs 97% vs 100%, vs 100%, vs 95.5%, respectively, $P=0.3$). In Cox proportional hazard analysis when age at diagnosis, tumour size, lymph node, capsular and tissue invasion were taken into account the only predictor for disease progression was lymph node invasion (HR 0.039, 95% CI 0.004–0.379, $P=0.005$). Similar results were found when only those who underwent ablation with ^{131}I were examined. 10.3% of patients with lymph node invasion showed disease progression; all belonged to group 5 ($P=0.038$, Pearson χ^2).
Conclusions
Although, patients with tumours ≥ 0.9 cm have more frequently disease persistence, the final outcome is similar in all mPTC groups. Lymph node invasion may be the only factor predicting disease progression in mPTCs.
DOI: 10.1530/endoabs.37.GP.27.03

GP.27.04

TIM16 inhibition enhances sensitivity to paclitaxel and decreases calcitonin secretion by reducing mitochondrial membrane potential in a human medullary thyroid carcinoma cell line

Teresa Gagliano[1], Eleonora Riva[1], Federico Tagliati[1], Daniele Matteotti[1], Valentina Brugnoli[1], Silvia Sambugaro[1], Marta Bondanelli[1], Erica Gentilin[1], Simona Falletta[1], Katiuscia Benfini[1], Carmelina Di Pasquale[1], Remo Guerrini[2], Severo Salvadori[2], Ettore degli Uberti[1] & Maria Chiara Zatelli[1]
[1]Section of Endocrinology and Internal Medicine, Department of Medical Science, University of Ferrara, Ferrara, Italy; [2]Department of Chemical and Pharmaceutical, University of Ferrara, Ferrara, Italy.

TIM16, a protein of the translocase complex TIM23 of the mitochondrial inner membrane, is encoded by the Magmas a gene. Magmas silencing has been associated with a greater sensitivity to apoptotic stimuli in pituitary adenoma cell lines. We recently demonstrated that in a human medullary thyroid carcinoma cell line (TT) compound 5, a TIM16 inhibitor, was not cytotoxic but enhanced the proapoptotic effects of staurosporine. The aim of our study is to verify whether mithocondrial function is involved in compound 5 effects. To evaluate cell viability we performed ATPlite assay, while caspase 3/7 assay was used to determine apoptotic activation. ELISA test was used for calcitonin detection in cell culture medium, while TMRM assay was employed to evaluate mitochondrial membrane potential (MMP). Our data show that paclitaxel 10 nM was reduced cell viability by 40%, while compound 5 alone had no effects. However, compound 5 was able to significantly increase the effects of paclitaxel by nearly 14%. In addition, paclitaxel increased caspase 3/7 activity by 130%, which was further increased by co-incubation with compound 5. In addition, we found that compound 5 was able to reduce basal and pentagastrin induced calcitonin secretion. Furthermore, compound 5 and paclitaxel decreased MMP (by -15 and -20% vs CT respectively), and their combination was even more potent (-50% vs CT). In conclusion, compound 5 could represent a tool to increase the effects of chemotherapeutic agents and to control hypercalcitoninemia in medullary thyroid carcinoma.

DOI: 10.1530/endoabs.37.GP.27.04

GP.27.05

Effect of a very low dose of rituximab on active moderate–severe Graves' orbitopathy: an interim report

Guia Vannucchi[1], Irene Campi[1], Danila Covelli[1], Nicola Currò[2], Davide Dazzi[3], Sabrina Avignone[4], Clara Sina[4], Claudio Guastella[5], Lorenzo Pignataro[5] & Mario Salvi[1]
[1]Endocrine Unit, Fondazione IRCCS Cà Granda, Milan, Italy; [2]Ophthalmology, Fondazione IRCCS Cà Granda, Milan, Italy; [3]Neuroradiology, Fondazione IRCCS Cà Granda, Milan, Italy; [4]Otolaryngology, Fondazione IRCCS Cà Granda, Milan, Italy; [5]Internal Medicine, Ospedale di Fidenza, Fidenza, Italy.

Previous studies have shown that Rituximab (RTX) is effective as a disease modifying drug at doses of 500 mg or 1000×2 mg in active Graves' orbitopathy (GO). We have conducted a pilot study (EUDRACT 2012-001980-53) in which patients with active moderate-severe GO were treated with a single infusion of low dose RTX (100 mg). Ten patients were enrolled of whom seven completed the study at 52 weeks. Five patients did not respond to a previous treatment with i.v. methylprednisolone, whereas five had newly diagnosed GO. Disease activity was assessed with the clinical activity score (CAS) and severity with NOSPECS score. The primary endpoint was the decrease of the CAS of 2 points or CAS ≤3.

Results

Of the seven patients who completed the study, six had inactive disease at 12 weeks (ANOVA, $P=0.01$); one was submitted to surgical orbital decompression because of signs of optic neuropathy (ON). Another patient, although who had disease inactivation at 12 weeks, underwent surgical orbital decompression at 22 weeks because of suspected subclinical ON. At 24 weeks four patients were inactive (ANOVA, $P=0.001$); one had a transient disease reactivation with stabilization at 40 weeks. The treatment was well tolerated with only minor infusion-related reactions.

Conclusion

Very low dose of RTX seems effective in disease inactivation but may not modify the natural course of disease as has been observed with higher therapeutic doses.

DOI: 10.1530/endoabs.37.GP.27.05

GP.27.06

hCG levels are essential for the correct interpretation of gestational TSH levels: the clinical risk assessment of premature delivery

Tim Korevaar, Marco Medici, Layal Chaker, Henning Tiemeier, Theo Visser & Robin Peeters
Erasmus University Medical Center, Rotterdam, The Netherlands.

Context

High maternal TSH and/or low FT_4 during pregnancy is associated with an increased risk of premature delivery. hCG is the main determinant of thyroid function changes during pregnancy but has a versatile pattern with high inter and intra-individual variability. We hypothesised that the correct interpretation of thyroid function tests and its use in the risk assessment of premature delivery during pregnancy depend on hCG levels.

Design, setting, and participants

TSH, FT_4, hCG, and TPO-antibody levels were available in 5956 women. In logistic regression models for premature delivery we tested for interaction between TSH or FT_4 and hCG and when significant analyses were stratified. All analyses were adjusted for maternal age, smoking, education level, ethnicity, parity, BMI, height, and foetal gender.

Results

The association between TSH levels and premature delivery was different according to hCG levels (P interaction $=0.02$). The risk of premature delivery in women with high TSH levels $\geq$85th, $\geq$90th, or $\geq$95th percentile but low hCG levels was decreased by 47, 61, and 18% respectively. The risk of premature delivery in women with high TSH levels $\geq$85th, $\geq$90th, or $\geq$95th percentile but high hCG levels was increased two-, 3.1-, and 6.1-fold respectively (P low vs high <0.001). The association between FT_4 levels and premature delivery was not different according to hCG levels (P interaction $=0.23$). However, women with very low FT_4 levels ($\leq$3rd percentile) had different risks for premature delivery according to hCG (low to high OR 1.99–3.11; $P=0.02$). All results remained similar after exclusion of TPOAb positive women, women with preeclampsia or amongst women with spontaneous premature delivery only.

Conclusion

The addition of hCG may improve the risk assessment of premature delivery according to TSH. High TSH levels despite high hCG levels reflect the inability of thyroid function to increase according to hCG stimulation. This inability to increase is a novel risk factor for premature delivery. Future studies are needed to replicate these results and incorporate these findings into clinical decision models.

Disclosure

This work was supported by a clinical fellowship from ZonMw, project number 90700412 (R Peeters).

DOI: 10.1530/endoabs.37.GP.27.06

GP.27.07

Plasmapheresis in thyroid storm caused by exogenous thyroid hormone intake: a case series

Tiago Nunes da Silva[1], Bernardo Dias Pereira[1], Henrique Vara Luiz[1], Ricardo Macau[2], Ana Catarina Matos[1], Isabel Manita[1], Pedro Bravo[2], Maria Carlos Cordeiro[1], Luisa Raimundo[1] & Jorge Portugal[1]
[1]Hospital Garcia de Orta–Endocrinologia e Diabetes, Almada, Portugal; [2]Hospital Garcia de Orta–Nefrologia, Almada, Portugal.

Thyroid storm (TS) is one extreme of a continuum beginning with thyrotoxicosis. It's rarely caused by exogenous thyroid hormone intake (ETHI). Aggressive medical therapy is the cornerstone of treatment; nevertheless, it might not be sufficient. Plasmapheresis is an extracorporeal technique that can rapidly lower thyroid hormone levels. The aim of this study was to assess the efficacy of plasmapheresis in TS secondary to ETHI. We evaluated retrospectively all TS cases (Burch–Wartofsky score >45) caused by ETHI, treated with plasmapheresis between 1991 and 2014 in a tertiary hospital. Patient clinical data, normal thyroglobulin and negative anti-thyroglobulin antibodies ruled out endogenous causes. Statistical analysis was performed with Wilcoxon's test (SPSS v.21).

Five cases were recorded. The median age was 45 years and four patients were female. The Burch–Wartofsky score ranged from 50 to 85. All patients presented with delirium, the median heart rate was 134 b.p.m. and four patients required an intensive care unit because of hemodynamic instability. Standard medical therapy for TS was initiated on admission. Plasmapheresis sessions ranged from 3 to 4 and were started between days 2 and 5 after admission. Before the first plasmapheresis, median TT_4 was 70 μg/dl (4.5–12.5), FT_4 17.2 ng/dl (0.8–1.5), TT_3 1800 ng/dl (80–200), and FT_3 46 pg/ml (1.5–5). The first session induced a significant decrease in median TT_4 and FT_4 levels of 40 and 46% respectively ($P=0.043$). After the last session, a significant large decrease in all thyroid hormone levels was observed: TT_4 – 75%, FT_4 – 72%, TT_3 – 92%, and FT_3 – 85%. ($Z=-2.023$, $P=0.043$, $r=0.64$). Euthyroidism was achieved after a median of 12 days.

Our study showed that plasmapheresis induced a significant and rapid decrease in hormone levels, allowing all the patients to recover. It should be considered as a second line therapy for refractory TS induced by ETHI and should be started relatively soon in the treatment algorithm.

DOI: 10.1530/endoabs.37.GP.27.07

GP.27.08

There is a detectable immune activity in the orbits of all patients diagnosed with Graves' disease regardless of later development of Graves' orbitopathy

Eszter Berta[1,2], Bernadett Újhelyi[4], Lajos Szabados[3], László Galuska[3], Annamária Erdei[1], Annamária Gazdag[1], Sándor Halmi[1,2], Endre Nagy[1] & Miklós Bodor[1,2]
[1]Division of Endocrinology, Department of Medicine, University of Debrecen, Debrecen, Hungary; [2]Department of Clinical Pharmacology, University of Debrecen, Debrecen, Hungary; [3]Department of Nuclear Medicine, University of Debrecen, Debrecen, Hungary; [4]Department of Ophthalmology, University of Debrecen, Debrecen, Hungary.

Graves' orbitopathy (GO) is a common complication of Graves' disease (GD) which is often responding poorly to therapy. GO may develop before or together with, or during the course of GD. In an individual patient, the development of GO cannot be predicted. We assumed that orbital autoimmune activity is predictable using orbital 99mTc-labelled diethylenetriamine pentaacetic acid (99mTc-DTPA) SPECT. We aimed to determine whether any orbital autoimmune activity can be identified in patients who do not develop GO during their follow-up. Fifty-four orbits of 27 patients newly diagnosed with GD were entered into the study. Patients with present GO were excluded. None of the patients had received antithyroid drugs or ophthalmic measures before entering the study. An initial 99mTc-DTPA SPECT was performed and DTPA uptake as sign of disease activity calculated in each case. SPECT was repeated during follow-up if clinical signs of GO occurred, and a final SPECT was performed at the end of the follow-up period, after 1 year. Twenty orbits of control patients who underwent DTPA SPECT of the hands for Raynaud's phenomenon served as controls. During the 2-year follow-up, six out of the 27 patients (22%) were diagnosed with newly developed GO. The mean initial DTPA uptake of the orbits of GD patients with or without later developing GO was significantly higher than results obtained from the control group (10.45 ± 1.72, 9.18 ± 1.18, and 7.7 ± 2.44 MBq/cm^3, respectively, $P < 0.05$). Initial DTPA uptake values of the six patients who later developed GO were not different from the rest of the GD group. All GD patients have mild orbital activity signs by the DTPA technique in the early stage of GD, irrespective of development or lack of GO during the course of GD. This uniform ongoing subclinical inflammation may be a reversible early stage of GO.

DOI: 10.1530/endoabs.37.GP.27.08

Endocrine tumours and neoplasia - NETS

GP.28.01

Clinicopathologic features, treatments, and survival of patients with ectopic Cushing's syndrome from neuroendocrine tumours: data from an Italian multicentre study

Maria Vittoria Davi[1], Elisa Cosaro[1], Serena Piacentini[2], Giuseppe Reimondo[3], Nora Albiger[4], Giorgio Arnaldi[5], Antongiulio Faggiano[6], Giovanna Mantovani[7], Nicola Fazio[8], Franco Grimaldi[9], Massimo Mannelli[10], Francesca Pecori Giraldi[11], Chiara Martini[12], Diego Ferone[13], Davide Campana[14], Carla Scaroni[4], Massimo Terzolo[3], Laura DeMarinis[2] & Giuseppe Francia[1]
[1]University of Verona, Verona, Italy; [2]Catholic University of Sacred Heart, Rome, Italy; [3]University of Turin, Turin, Italy; [4]Endocrinology, University of Padua, Padua, Italy; [5]Polytechnic University of Marche Region, Ancona, Italy; [6]Federico II University of Naples, Naples, Italy; [7]Endocrinology, University of Milan, Milan, Italy; [8]European Oncologic Institute, Milan, Italy; [9]S. Maria della Misericordia Hospital, Udine, Italy; [10]University of Florence, Florence, Italy; [11]Istituto Auxologico Italiano, University of Milan, Milan, Italy; [12]Clinica Medica III, University of Padua, Padua, Italy; [13]University of Genoa, Genoa, Italy; [14]University of Bologna, Bologna, Italy.

Introduction
Available literature on series of patients affected by ectopic Cushing's syndrome (ECS) deriving from neuroendocrine tumours (NETs) is relatively scarce. This is the first Italian multicentre study regarding clinicopathologic features, modalities of treatment, and survival of patients with NETs and ECS.

Patients and methods
Retrospective analysis of data from patients with ECS from NETs collected in 14 centres between 1986 and 2014, obtained by a specific questionnaire.
Results
96 patients, 58.3% females, mean (S.D.) age at diagnosis 50.4 ± 15 years. Clinical presentation included hypertension (87%), diabetes mellitus (67%), proximal myopathy (67.7%), weight loss (28.1%), skin fragility (53%), hypercoagulopathy (28%), osteoporosis (47%), and psychiatric disease (32.3%). Regarding prevalence of NETs, 42.7% were bronchial carcinoids, 3.1% small-cell lung carcinoma (SCLC), 13.5% pancreatic (p), 8.3% thymic, 4.2% phaeochromocytoma, 5.2% others, and 23% occult. Tumour diameter of p-NETs was larger than that of bronchial carcinoids (47.3 ± 34 mm vs 28 ± 21.4 mm, P 0.035). Distant metastases were more prevalent in p-NETs, SCLC and thymic than in bronchial carcinoids and occult (77.7, 66.7, 50% vs 24.4, 13.6% respectively). Among 45 NETs with available Ki67, 46.7% were G1, 37.8% G2 and 15.6% G3. Immunostaining for ACTH was positive in 85.4%. Surgery was performed in 54,1%, steroidogenesis inhibitors in 77.1%, somatostatin analogues in 53.1%, cabergoline in 9.4%, mifepristone in 1%, everolimus in 6.2%, sunitinib in 1%, chemotherapy in 23%, PRRT in 10.4%, mono/bilateral adrenalectomy in 29%, and interventional treatments of liver metastases in 5.2%. Mean survival was 78 months (range 1–276), 24% died due to NET.
Conclusions
Bronchial carcinoids are the main NET associated with ECS, whereas 23% of cases are still occult. p-NETs are larger than bronchial carcinoids and more aggressive. Hystopathology, grading and distant metastases are the main prognostic factors. A multimodal treatment, including surgery of NET whenever possible, and adrenalectomy to definitively solve hypercortisolism thus reducing the risk of complications, can prolong survival.

DOI: 10.1530/endoabs.37.GP.28.01

GP.28.02

Localisation of insulinoma: comparison of glucagon-like peptide 1 receptor SPECT/CT, PET/CT, and MRI: preliminary results of a prospective clinical study

Kwadwo Antwi[1], Melpomeni Fani[1], Tobias Heye[1], Guillaume Nicolas[1], Elmar Merkle[1], Jean Claude Reubi[2], Beat Gloor[3], Stefan Fischli[4], Damian Wild[1] & Emanuel Christ[5]
[1]Clinic of Radiology and Nuclear Medicine, University of Basel Hospital, Basel, Switzerland; [2]Division of Experimental Pathology, Department of Pathology, University of Bern, Bern, Switzerland; [3]Department of Visceral Surgery, University Hospital of Bern, Inselspital, Bern, Switzerland; [4]Division of Endocrinology, Diabetology and Clinical Nutrition, Hospital of Luzern, Luzern, Switzerland; [5]Division of Endocrinology, Diabetology and Clinical Nutrition, University Hospital of Bern, Inselspital, Bern, Switzerland.

Purpose
We aim at prospectively comparing the detection rate of glucagon-like peptide 1 receptor (GLP1R) PET/CT vs GLP1R SPECT/CT vs standardised contrast enhanced 3T MRI in patients with endogenous hyperinsulinaemic hypoglycaemia.
Methods
14 patients with neuroglycopenic symptoms due to endogenous hyperinsulinaemic hypoglycaemia were already enrolled (mean age 56 years, ten females and four males). A standardized contrast enhanced 3T MRI was performed. Afterwards the patients received a SPECT/CT at 4 and 72 h after injection of ^{111}In-DOTA-exendin-4 and a PET/CT 2.5 h after injection of ^{68}Ga-DOTA-exendin-4, in a randomized order. Standard of comparison was the histological diagnosis after surgery.
Results
In 11 patients histological diagnosis confirmed benign insulinoma, one patient had adult nesidioblastosis. In one patient none of the imaging modalities were able to find any lesion. Another patient refused surgery despite a positive PET/CT scan. In 8/12 patients previously performed conventional imaging (CT/MRI) was not able to localise the insulinoma. Standardized 3T MRI was able to predict the correct localisation of the insulinoma in 8/12 patients. PET/CT correctly identified the insulinoma or nesidioblastosis in 12/12 patients whereas SPECT/CT correctly identified the insulinoma in 10/12 patients. PET/CT was the only modality which identified the region of islet cell hyperplasia (adult nesidioblastosis) within the pancreas.
Conclusion
GLP1R PET/CT defines a novel, non-invasive, highly sensitive tool in localizing insulinomas. Standardised contrast enhanced MRI improves the diagnostic accuracy compared to locally performed conventional imaging. Further studies will have to confirm whether PET/CT is able to localise adult nesidioblastosis.
Disclosure
This work was supported in part by the Swiss National Science Foundation grant number 320030_152938/1 (to E Christ, D Wild, and M Fani) and the Desirée and Niels Yde's Foundation Grant No, 389-12 (to D Wild).

DOI: 10.1530/endoabs.37.GP.28.02

GP.28.03

Could ^{99m}Tc labelled glucagon-like peptide 1 analogue scintigraphy be an answer for patients with persistent hypoglycaemia?

Alicja Hubalewska-Dydejczyk[1], Anna Sowa-Staszczak[1], Agnieszka Stefanska[1], Dorota Pach[1], Monika Buziak-Bereza[1], Małgorzata Trofimiuk-Müldner[1], Aleksandra Gilis-Januszewska[1], Agata Jabrocka-Hybel[1], Monika Tomaszuk[1], Romana Tomaszewska[2], Maciej Malecki[3], Tomasz Bednarczuk[4], Grzegorz Kaminski[5], Aldona Kowalska[6], Renata Mikolajczak[7] & Barbara Janota[7]
[1]Department of Endocrinology, Jagiellonian University Medical College, Krakow, Poland; [2]Department of Pathology, Jagiellonian University Medical College, Krakow, Poland; [3]Department of Metabolic Diseases, Jagiellonian University Medical College, Krakow, Poland; [4]Department of Endocrinology, Medical University of Warsaw, Warsaw, Poland; [5]Department of Endocrinology and Radioisotopic Therapy, Military Institute of Medicine, Warsaw, Poland; [6]Department of Endocrinology and Nuclear Medicine, Holycross Cancer Center, Kielce, Poland; [7]Radioisotope Center POLATOM, National Centre for Nuclear Research, Otwock, Poland.

Surgery is the only effective therapy for insulinoma patients, therefore there is a necessity to develop diagnostic strategies in cases of unknown tumour location, possibly through the use of new biomarkers. ^{99m}Tc labelled glucagon-like peptide 1 analogue (^{99m}Tc-GLP1) scintigraphy has been developed in our centre as an imaging technique of insulinoma. Labelled GLP1 analogue might also be applied in diagnosis of various forms of nesidioblastosis allowing to determine the range of surgery in its focal and diffuse types, if suitable.
Material and methods
Study included: 40 patients with suspected insulinoma in whom CT/MR/EUS/SRS failed to visualise tumour thus excluding surgical intervention, 3patients with malignant insulinoma and three with nesidioblastosis (to assess its type form). (Lys^{40}(Ahx-HYNIC-^{99m}Tc/EDDA)NH_2)exendin-4-SPECT/CT with volumetric analysis was performed.
Results
21/40 cases were true positive with focal tracer uptake in pancreas including histopathologically confirmed bifocal insulinoma. In all operated patients symptoms resolved postsurgically. One false negative result appeared to be malignant insulinoma, in one no tumour was found (false positive result). Nine cases were true negative with no ^{99m}Tc-GLP1 uptake (reactive hypoglycemia or Munchausen syndrome); eight patients were lost from follow up. Sensitivity, specificity, PPV of ^{99m}Tc-GLP1-SPECT/CT were 95, 90, and 95% respectively. Scintigraphy revealed diffuse tracer uptake in two, and a focal lesion in one nesidioblastosis patients (histopathology: coexistent nesidioblastosis and insulinoma). ^{99m}Tc-GLP1–SPECT/CT confirmed different biology of primary tumour (PT) and metastases in malignant insulinoma (phenomenon well known in NENs): both PT and metastases were negative in one patient, PT positive and metastases negative in 1, PT negative and metastases positive in last case.
Conclusions
In our study ^{99m}Tc-GLP1–SPECT/CT proved to be helpful in management of persistent hypoglycaemia patients. ^{99m}Tc-GLP1–SPECT/CT could also be considered in the former stages of diagnostic schemes to optimise the procedures with a more effective strategy to allow sparing operation as well as to improve the quality of life of these patients.
Disclosure
This study was supported by the Polish Ministry of Science within Research project number N402 445039.

DOI: 10.1530/endoabs.37.GP.28.03

GP.28.04

Receptor tyrosine kinase expression and their role in the response to target therapy in bronchopulmonary NET

Tersa Gagliano, Katiusci Benfini, Erica Gentilin, Simona Falletta, Marta Bondanelli, Carmelina Di Pasquale, Eleonora Riva, Ettore degli Ubertu & Maria Chiara Zatelli
Section of Endocrinology and Internal Medicine, Department of Medical Science, University of Ferrara, Ferrara, Italy.

Surgery is not feasible for infiltrating and metastatic bronchopulmonary NET (BP-NET). In those cases, medical therapy is tried with controversial results. Thus, it is important to identify new therapeutic targets to provide adequate medical treatment for patients with BP-NET. Sunitinib, is a multi-targeted receptor tyrosine kinase inhibitor (TKI), mainly described to inhibit VEGFR.
The aim of our study is to verify whether insulin receptor (IR), IGF1R, and EGFR could be involved in Sunitinib mechanism of action in BP-NET cells.
For this purpose human BP-NET cell lines and human BP-NET primary cultures were treated with Sunitinib and/or EGF, IGF1, or VEGF. Cell viability and caspase 3/7 activation were measured after 48 h of treatment. Receptor expression was detected by Western blot in both cell lines and primary cultures. Phosphorylation of IGF1R and EGFR was analysed by Alphascreen sure fire assay.
Our results show that Sunitinib is capable of inhibiting cell viability of BP-NET cell lines and primary cultures, and activates caspase 3/7. Both events are counteracted by EGF and IGF1, but not by VEGF. Moreover, both cell lines and tissues invariably express IR, IGF1, and EGFR, while VEGFRs are expressed only in some samples. Treatment with Sunitinib decreased the phosphorylation of both EGFR and IGFR1, in both cell lines and primary cultures.
In conclusion, these data indicate that the expression of EGFR and IGF1R are important for Sunitinib action in BP-NET. The effects of Sunitinib on BP-NET cell viability could be due to a double inhibition of EGFR and IGF1R, while the role of IR needs to be further investigated.

DOI: 10.1530/endoabs.37.GP.28.04

GP.28.05

Filamin-A is involved in stabilisation, signal transduction, and angiogenesis regulation mediated by somatostatin receptor 2 in pancreatic neuroendocrine tumors

Eleonora Vitali[1], Valeria Cambiaghi[1], Federica Loiarro[1], Alessandro Zerbi[2], Piergiuseppe Colombo[3], Anna Spada[4], Giovanna Mantovani[4], Erika Peverelli[4], Carlo Carnaghi[5] & Andrea Lania[1,6]
[1]Laboratory of Cellular and Molecular Endocrinology, IRCCS Clinical and Research Institute Humanitas, Rozzano, Milan, Italy; [2]Pancreas Surgery Unit, IRCCS Humanitas Clinical Institute, Rozzano, Milan, Italy; [3]Department of Pathology, IRCCS Humanitas Clinical Institute, Rozzano, Milan, Italy; [4]Endocrine Unit, Department of Clinical Sciences and Community Health, Fondazione IRCCS Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; [5]Medical Oncology and Hematology Unit, Cancer Center, Humanitas Clinical and Research Center, Rozzano, Milan, Italy; [6]Biometra Department, Neurosurgery Department, IRCCS Humanitas Clinical Institute, University of Milan, Rozzano, Milan, Italy.

Somatostatin receptor type 2 (SST2) is the main pharmacological target of long-acting somatostatin analogues (SSA) widely used in patients with pancreatic neuroendocrine tumours (P-NETs). A subset of patients is resistant to SSA, although the molecular mechanisms responsible for resistance are poorly understood. Several studies identified cytoskeleton protein interactions as determinant in receptor anchoring, expression and signalling. Since SST2 was recently demonstrated to associate to filamin A (FLNA), we investigated the role of this cytoskeleton protein in SST2 expression, signalling and angiogenesis in human P-NETs and in QGP1 cell lines. We found no correlation between FLNA and SST2 expression in P-NETs, confirming this, FLNA knockdown did not induce changes in SST2 levels in QGP1 cells. Conversely, a significant reduction in SST2 expression was observed in FLNA silenced cells after selective long term SST2 activation with BIM23120 ($-49\pm17\%$, $P<0.05$ vs basal). To evaluate the role of FLNA on SST2 signalling, we analysed cyclin D1 expression, ERK1/2 phosphorylation, and cAMP accumulation. Interestingly, the reduction in cyclin D1 levels ($-44\pm22\%$, $P<0.05$ vs basal) and ERK1/2 phosphorylation ($-59\pm18\%$, $P<0.05$ vs basal) induced by SST2 agonist (BIM23120) was abolished in FLNA-silenced QGP1 cells. Similarly, BIM23120 inhibited forskolin-stimulated cAMP accumulation in cells transfected with negative control and this effect was abrogated in FLNA silenced cells. In addition, BIM23120 incubation induced a decrease in both VEGF expression ($-31\pm7\%$ in negative control transfected cells, $P<0.001$ vs untreated cells) and VEGF release into control cell supernatants ($-39\pm24\%$, $P<0.05$ vs untreated cells) and these effects being completely abolished by FLNA silencing. In conclusion, these results demonstrate that FLNA is required for SST2 stabilisation, signalling and angiogenesis in tumoural pancreatic neuroendocrine cells, thus suggesting a possible role of this cytoskeleton protein in determining the different responsiveness to SSA observed in P-NET patients.
Disclosure
This work was supported by an AIRC (Associazione Italiana Ricerca Cancro – Milan) grant number KFR062-2 to Adrea Lania and by Ricerca Funds by Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico.

DOI: 10.1530/endoabs.37.GP.28.05

GP.28.06

Patient-reported time to diagnosis of neuroendocrine tumors (NETs) in Europe: results from the first global NET patient survey: a collaboration between the International Neuroendocrine Cancer Alliance (INCA) and Novartis

Marianne Pavel[1], Teodora Kolarova[2], Grace Goldstein[3], John Leyden[4] & Maia Sissons[5]
[1]Charité Universitätsmedizin Berlin, Berlin, Germany; [2]APOZ and Friends, Sofia, Bulgaria; [3]The Carcinoid Cancer Foundation, Inc., White Plains, New York, New York, USA; [4]The Unicorn Foundation, Mosman, New South Wales, Australia; [5]NET Patient Foundation, Hockley Heath, UK.

Background
Neuroendocrine tumor (NET) symptoms are often similar to common conditions or may not arise until metastasis occurs, delaying diagnosis and impacting survival. We present data on time to diagnosis from the European (EU) NET patient perspective.
Methods
In 2014, 1928 NET patients from >12 countries (Europe ($n=763$): Belgium, Bulgaria, France, Germany, Norway, UK, and other EU countries (not specified); Americas; Asia; Oceania) participated in a survey on the NET patient experience, including diagnosis, conducted by Hall and Partners on behalf of International Neuroendocrine Cancer Alliance (INCA)/Novartis and funded by Novartis. All comparisons were significant at $P<0.05$.
Results
60% of respondents reported being diagnosed <5 years ago; median time from symptom onset to diagnosis was 24 months (for overall population and patients diagnosed <5 years vs ≥5 years ago). Notably, 24% reported a ≥5-year lag for diagnosis. 63% had metastases at diagnosis (higher in patients diagnosed <5 years (67%) vs ≥5 years (57%) ago). Patients saw a mean of seven health care providers (HCPs) with a mean of 11 HCP visits prior to NET diagnosis. While 67% visited a NET specialty center (mean 4.7 times/year), only 25% were diagnosed there. For 43% of patients, NET was not the initial diagnosis, and 26% were diagnosed with NETs during testing for another condition. The most common early diagnoses were digestive disorders. Most patients (74%) did not suspect their symptoms were cancer related. Patients diagnosed <5 years ago felt more informed (able to get answers (65%)/had sufficient information (58%)) than those diagnosed ≥5 years ago (56%/48% respectively). The majority (65%) felt there was much room for improvement in NET diagnosis: 52% wanted clearer information about long-term impact; 42% wanted better direction regarding NET-related information.
Conclusion
This large global NET patient survey demonstrated delays in NET diagnosis in EU patients, consistent with global findings in the literature, and identified areas for improvement.
Disclosure
The Global NET Patient Survey was conducted as a collaboration between the INCA and Novartis Pharmaceuticals. Funding for this survey was provided by Novartis.

DOI: 10.1530/endoabs.37.GP.28.06

GP.28.07

Complete remission of hepatic metastasis after total gastrectomy for a gastric carcinoid tumor type 1: a case report

Alberto Stefano Tresoldi[1], Cristina Bonifacio[2], Giovanna Pepe[3], Carlo Carnaghi[4] & Andrea Gerardo Antonio Lania[1,5]
[1]Department of Endocrinology, Humanitas Clinical and Research Center, Rozzano (MI), Italy; [2]Department of Radiology, Humanitas Clinical and Research Center, Rozzano (MI), Italy; [3]Department of Nuclear Medicine, Humanitas Clinical and Research Center, Rozzano (MI), Italy; [4]Department of Oncology, Humanitas Clinical and Research Center, Rozzano (MI), Italy; [5]Department of Biotechnologies and Translational Medicine, Milano (MI), Italy.

Gastric carcinoids secondary to autoimmune atrophic gastritis (GC type 1) are usually well differentiated neoplasia, with an indolent course and an excellent overall prognosis. However, a subset of these tumors (<5%) may develop advanced disease, with lymph node and/or hepatic metastasis. The pathogenesis of these carcinoids is related to chronic trophic stimuli to enterochromaffin-like (ECL) cells due to chronic hypergastrinemia. Treatments directed to remove the source of hypergastrinemia (such as antrectomy and SSAs) have been used with good results in localized tumors. These approaches had been used in localized disease, while its effectiveness had never been demonstrated in metastatic cases. In this report, we describe the case of a woman with type 1 gastric carcinoid with liver metastasis documented by abdominal CT and ^{68}Ga-PET DOTATOC. The patient underwent total gastrectomy with lymph node dissection; during surgery an hepatic US was performed, showing seven subcentimeter metastases. Histological examination revealed a neuroendocrine neoplasm G2 (WHO 2010) of 30 mm, Ki67 20%, 15 mitoses/10 HPF; chronic gastritis and micronodular hyperplasia of endocrine cells was associated. During the early months of follow up a gradual reduction in size of liver metastases, until the complete disappearance of them was observed. This is to our knowledge the first case ever described in literature of complete remission of liver metastatic type 1 GC after removal of the source of excessive gastrin, showing a possible preservation of responsiveness of metastases to gastrinemic stimuli. This could lead to a possible change in therapeutic approach in these neoplasm.

DOI: 10.1530/endoabs.37.GP.28.07

GP.28.08

General characteristics and evaluation of β-cell function and insulin sensitivity in a large monocentric series of insulinomas

Raluca Maria Furnica, Laure Istasse, Jean-Francois Gigot, Pierre Deprez, Martin Buysschaert & Dominique Maiter
Cliniques Universitaires Saint Luc, Brussels, Belgium.

Background
Insulinomas are the most common functional neuroendocrine tumours of the pancreas. Hypoglycaemic manifestations are highly variable and largely independent on tumour size and severity of insulin hypersecretion.
Objectives
In this study we investigated the clinical, biological and tumoural characteristics of a large series of patients with insulinoma and we evaluated the sensitivity of peripheral tissues to insulin before and after surgery.
Patients and methods
This is a retrospective analysis of 40 patients followed between 1982 and 2012 in our academic hospital. Insulin sensitivity and β-cell function could be evaluated by HOMA test in a subset of these patients.
Results
The mean age at onset of symptoms was 48.8±20.1 years and the mean age at diagnosis was 50.7±19.9 years. A sex ratio of 0.6 (15 men for 25 women) was found. Adrenergic symptoms were observed in 75% of patients and neuroglucopenic symptoms in 90%. In addition, 33% of patients suffered from epileptic disorders and 20% from psychiatric manifestations. Weight gain was observed in 40% of the patients. The most effective imaging techniques to localize the tumour were endoscopic ultrasound (90% sensitivity) and intraoperative ultrasound (94% sensitivity). Insulin sensitivity (measured outside hypoglycaemic episodes) was greatly reduced in patients with insulinoma (38.9± 22.3%), while β-cell function was increased (359.0±171.5%), but to a variable extent (range 110.6–678.6%). After complete resection of the tumour and disappearance of hypoglycaemia, insulin sensitivity normalizes from 36.9±19.0 to 80.6±18.4% ($P<0.001$) in 12 cured patients with available pre- and post-operative HOMA tests.
Conclusion
The general characteristics of our series are consistent with the general features reported for insulinomas in the literature. We also show that in response to chronic hyperinsulinaemia, patients with insulinoma develop protective mechanisms responsible for a marked insulin resistance, which is fully reversible after complete resection of the tumour.

DOI: 10.1530/endoabs.37.GP.28.08

GP.28.09

Association of angiopoietin/TIE2 plasma level and VEGF system with progression in gastroenteropancreatic neuroendocrine tumors

Miguel Sampedro-Nuñez[1,4], Ana Ramos-Leví[1,4], Alicia Vicuña[1], Sandra Campos[1], Ana Serrano[1,4], Ana Rodríguez-Muñoz[1,4], Rebeca Martínez-Hernández[1,4], Elena Martín-Pérez[2,4], Magdalena Adrados[3,4] & Mónica Marazuela[1,4]
[1]Department of Endocrinology and Nutrition, Hospital Universitario de la Princesa, Madrid, Spain; [2]Department of General and Gastrointestinal Surgery, Hospital Universitario de la Princesa, Madrid, Spain; [3]Department of Pathology, Hospital Universitario de la Princesa, Madrid, Spain; [4]Universidad Autónoma de Madrid, Instituto de Investigación Sanitaria Princesa, Madrid, Spain.

Introduction
Angiopoietins (ANG) -1 and 2, their receptor TIE2, and the vascular endothelial growth factor (VEGF) are involved in the process of angiogenesis. However, their

role in the pathogenesis and development of gastroenteropancreatic neuroendocrine tumours (GEP-NETs) is not completely understood. In a previous study of 42 patients with GEP-NET, we observed an elevation of these serum markers, especially in those with metastatic disease. The objective of this study was to analyse the relationship between plasma levels of the ANG/TIE2-VEGF system in patients with GEP NETs who exhibited progression after 3 years of follow-up.
Methods and materials
26 Patients with GEP-NETs were studied. Primary location of tumours was pancreas ($n=13$) and intestine ($n=13$). Plasma levels of ANG-1, ANG-2, TIE2 and VEGF were determined by ELISA. We evaluated response to medical and/or surgical treatment using clinical and radiological criteria and patients were assigned to three categories (complete remission, stable disease or progressive response), accordingly. Statistical nonparametric analysis tests was performed.
Results
At diagnosis, 13 patients had positive regional lymph nodes and 13 distant metastases. Thirteen patients achieved complete response, six had stabilization and seven were classified as disease progression. Plasma TIE-2 levels at initial evaluation were higher in patients who had progressive disease (31 803.17 $\pm$ 5495.55 pg/ml) vs those who had complete response (18 930.00 $\pm$ 3914.20 pg/ml) or remained stable (25 236.67 $\pm$ 1072.40 pg/ml) ($P=0.012$). No differences were found in these angiogenic markers when comparing primary tumour location (pancreas or intestine), the presence or absence of metastases, or response to somatostatin analogue therapy.
Conclusion
TIE2 plasma values are higher in patients with GEP-NETs with progressive disease. This suggests a possible involvement of ANG/TIE2 system in the pathogenesis of GEP-NETs and a possible relevance as diagnostic and/or therapeutic target.

DOI: 10.1530/endoabs.37.GP.28.09

Endocrine tumours and neoplasia - Adrenal Tumour

GP.29.01

Mitotane inhibits sterol-o-acyltransferase leading to lipid-mediated endoplasmic reticulum stress and apoptosis of adrenocortical carcinoma cells

Silviu Sbiera[1,2], Martin Fassnacht[1,3], Ellen Leich[4], Gerhard Liebisch[5], Andreas Schirbel[6], Laura Wiemer[1], Silke Matysik[5], Jens T Vanselow[7], Felix Gardill[1], Annemarie Gehl[1], Sabine Kendl[1], Melanie Beyer[1], Margarita Bala[1], Cristina L Ronchi[1], Timo Deutschbein[1], Andreas Schlosser[7], Gerd Schmitz[6], Andreas Rosenwald[2,4], Bruno Allolio[1] & Matthias Kroiss[2]
[1]Endocrinology and Diabetes Unit, University Hospital Würzburg, Würzburg, Germany; [2]Comprehensive Cancer Center Mainfranken, Würzburg, Germany; [3]Clinical Chemistry and Laboratory Medicine, University Hospital Würzburg, Würzburg, Germany; [4]Institute of Pathology, University of Würzburg, Würzburg, Germany; [5]Institute of Clinical Chemistry and Laboratory Medicine, University Hospital Regensburg, Regensburg, Germany; [6]Department of Nuclear Medicine, University Hospital Würzburg, Würzburg, Germany; [7]Rudolf Virchow Center for Experimental Biomedicine, Würzburg, Germany.

Context
Mitotane is the only drug approved for treatment of adrenocortical carcinoma (ACC) and in clinical use for more than 50 years. Mitotane counteracts both tumour growth and tumoral steroid hormone production but treatment is associated with severe side effects. The molecular mechanism of mitotane is still unknown, which hampers progress in treatment of ACC.
Objective
To identify the mechanism of action and molecular target of mitotane.
Methods
We combined expression genomics, proteomics and lipidomics in an *in vitro* study using the NCI-H295 ACC reference cell line and four non-steroidogenic cell lines.
Results
Pathway analysis of gene expression data demonstrated activation of endoplasmic reticulum (ER) stress and altered lipid metabolism. Strongly increased expression of ER-stress marker C/EBP-homologous protein (CHOP, 26.7 $\pm$ 0.1-fold, $P<0.001$) and activated XBP1-mRNA splicing (23.2 $\pm$ 3.2-fold, $P<0.001$) was in sharp contrast to weak ER-stress activation in non-steroidogenic cell lines (HepG2: 2.6/1.4-fold, HEK293: 2.5/3.7, HeLa: 3.5/6.4, IMR-32: 1.5/2.1). ER-stress experimentally triggered by thapsigargin mimicked mitotane effects on steroidogenesis and apoptosis. Mass spectrometry revealed specific mitotane-induced lipid alterations with elevated free cholesterol (2.53-fold, $P<0.05$), oxysterols like 7-dehydrocholesterol (5.4-fold, $P<0.001$) and fatty acids, e.g. C20:4 (arachidonic acid; 3.2-fold, $P<0.01$) in NCI-H295 cells but not in other cell lines. Inhibition of Acyl-CoA-Cholesterol-Acyl-transferase (SOAT1) by mitotane (IC50 = 22 μM) was identified as the mechanism underlying these events.
Conclusions
Mitotane confers adrenal specific cytotoxicity and down-regulation of steroidogenesis by lipid-induced ER-stress through inhibition of SOAT-activity. This finding opens new avenues for improved ACC treatment. Cancer specific lipid metabolism may be a treatment target in other types of cancer.
Disclosure
This work was supported by Deutsche Forschungsgemeinschaft (grant FA 466/4-1 to M.F. and KR 4371/1-1 to M.K.), a fellowship of the Comprehensive Cancer Center Mainfranken to M.K., IZKF Würzburg (grant B-281 to M.F.), and the ERA-NET 'E-Rare'.

DOI: 10.1530/endoabs.37.GP.29.01

GP.29.02

Investigation of a novel liposomal chemotherapy protocol in three preclinical models for adrenocortical carcinoma *in vivo*

Sara Jung[1], Martin Reincke[1], Gerard P Zambetti[2], Felix Beuschlein[1] & Constanze Hantel[1]
[1]Endocrine Research Unit, Medizinische Klinik and Poliklinik IV, Ludwig-Maximilians-University, Munich, Bavaria, Germany; [2]Department of Biochemistry, St Jude Children's Research Hospital, Memphis, Tennessee, USA.

Recently, we demonstrated for adrenocortical carcinoma (ACC) promising antitumoural effects for LEDP-M (etoposide, liposomal doxorubicin, liposomal cisplatin, mitotane) a novel liposomal variant of the classical EDP-M protocol (etoposide, doxorubicin, cisplatin, mitotane). However, clinical translation of novel therapeutic regimens remains challenging due to high tumor heterogeneity. Thus, to obtain preclinical results with more clinically predictive power we investigated for the first time LEDP-M in three different xenograft models for ACC *in vivo*. Moreover, we included liposomal etoposide resulting in a novel treatment scheme called L(l)EDP-M. After one therapeutic cycle NCI-H295R, SW-13 and SJ-ACC3 tumours were excised and immunohistochemically (cells/high power fields (HPF)) analysed regarding total number of tumor cells (Ki67 positive and negative/HPF) and apoptosis (TUNEL positive cells/HPF). In previous experiments on NCI-H295R xenografts we detected a significant reduction in overall tumor cell count for LEDP-M which was in the current study not reached by L(l)EDP-M. In contrast, regarding apoptosis L(l)EDP-M ($P<0.01$) led to a further improvement of therapeutic efficacy as compared with LEDP-M ($P<0.05$ vs controls). In SW-13 xenografts, the number of tumor cells decreased in all treatment schemes with highest therapeutic efficacy of the liposomal variants (EDP-M: 20.5 $\pm$ 1.6 $P<0.01$; LEDP-M: 17.2 $\pm$ 1.3 $P<0.001$; L(l)EDP-M: 14.7 $\pm$ 0.9 $P<0.001$) vs. controls (28.9 $\pm$ 2.2). In addition, most distinctive necrosis was detectable for L(l)EDP-M followed by LEDP-M, EDP-M and controls. In SJ-ACC3 xenografts a decrease in tumor cell number was found only following EDP-M treatment (30.3 $\pm$ 1.2 vs controls 35.9 $\pm$ 1.3, $P<0.05$). In summary, these data indicate that liposomal regimens could represent promising treatment options for clinical translation for adult, but not for pediatric ACC. However, our results also show that tumor heterogeneity should be taken into account in preclinical studies.
Disclosure
This work was supported in part by the Wilhelm-Sander-Stiftung (2011.003.2) to C.H. and F.B.

DOI: 10.1530/endoabs.37.GP.29.02

GP.29.03

Immunoexpressions of CYP11B2 and HSD3B2 in genetically characterised aldosterone producing adenomas

Christian Gebhard[1], Yara Rhayem[1], Anna Dietz[1], Anna Riester[1], Constanze Hantel[1], Marion Schuster[1], Tim M Strom[2,3], Celso Gomez-Sanchez[4,5], Martin Reincke[1] & Felix Beuschlein[1]
[1]Medizinische Klinik und Poliklinik IV, Ludwig-Maximilians-University, Munich, Germany; [2]Institute of Human Genetics, Helmholtz Zentrum Munich, Munich, Germany; [3]Institute of Human Genetics, Technische Universität München, Munich, Germany; [4]Division of Endocrinology, G.V. (Sonny) Montgomery VA Medical Center, Jackson, Mississippi, USA; [5]Department of Medicine-Endocrinology, University of Mississippi Medical Center, Jackson, Mississippi, USA.

Primary aldosteronism caused by aldosterone-producing adenoma (APA) or bilateral adrenal hyperplasia is the most prevalent cause of secondary hypertension. Somatic mutations of *KCNJ5*, *ATP1A1*, *CACNA1D* and *ATP2B3* have been shown to be involved in the formation of APA. We studied the immunoexpressions of CYP11B2 and HSD3B2, the rate-limiting enzyme for aldosterone production and the prevalent isoform of β-HSD found in APA respectively, and correlated these findings with the mutation status, histopathology of APA and to the biochemical and clinical outcome of adrenalectomy. In our study, APA tissues obtained by adrenalectomy were divided into five subgroups (*KCNJ5*, *ATP1A1, CACNA1D, ATP2B3* or WT) after characterization of the respective mutational status by direct or exome sequencing. Paraffin-embedded tumors were evaluated for size and cell composition. Immunolocalization and semi-quantitative immunoexpressions of CYP11B2 and HSD3B2 were analysed. Scoring staining intensity was determined along with clinical findings. Our results show that a majority of APAs consists of both *zona fasciculata*-like and *zona glomerulosa* (*ZG*)-like cells. *CACNA1D* mutated-APA were significantly smaller than *KCNJ5* mutated-APA ($P<0.05$). All mutated APAs presented CYP11B2 positive clusters or variably stained scattered cells while WT APAs were weakly or negatively stained for CYP11B2 with only clusters in adjacent ZG. H-Score for CYP11B2 was significantly different between WT and *KCNJ5* mutated APAs ($P<0.05$). Immunoreactivity of HSD3B2 was strongly present in all analyzed tissues independently of the tumoural cell type and no significant difference was noted between the subgroups' HSD3B2 H-scores. Biochemically, serum potassium levels of all patients were normalized after adrenalectomy. High aldosterone to renin ratio at diagnosis and shorter duration of hypertension preceding surgery were associated with better clinical outcome. Our findings suggest that *KCNJ5* and not *ATP1A1, CACNA1D or ATP2B3* mutated APAs have significantly different CYP11B2 immunoreactivity, compared with WT-APA while immunoreacivities of HSD3B2 or CYP11B2 are not correlated with outcome.

Disclosure
ANR-DFG Genetik und Pathophysiologie des primären Aldosteronismus BE 2177/13-1.

DOI: 10.1530/endoabs.37.GP.29.03

GP.29.04

Synergistic action of 9-cis retinoic acid and mitotane in a H295R adrenocortical cancer xenograft model

Zoltan Nagy[1], Kornelia Baghy[1], Peter M Szabo[2], Ilona Kovalszky[1], Pal Perge[1], Attila Patocs[3], Karoly Racz[1] & Peter Igaz[1]
[1]Semmelweis University, Budapest, Hungary; [2]National Cancer Institute, Bethesda, Maryland, USA; [3]'Lendulet-2013' Hereditary Endocrine Tumours Research Group, Budapest, Hungary.

Background
Current drug treatment options for adrenocortical carcinoma (ACC) are rather limited and intensive efforts are going on to find novel effective agents. In our previous functional genomics study, retinoid signalling via the retinoid X receptor (RXR) was identified as a major pathogenic pathway in ACC and we have demonstrated the *in vitro* activity of 9-cis retinoic acid (9-cisRA) acting via the RXR on NCI-H295R cells and also found that 9-cisRA has antitumoural effects in a small pilot xenograft study.
Aim
To investigate the antitumoural effect of 9-cisRA and its combination with mitotane in a large-scale xenograft study.
Methods
43 male SCID mice xenografted with NCI-H295R cells were treated in four groups (i) control – corn oil vehicle, ii) 5 mg/kg 9-cisRA, iii) 200 mg/kg mitotane, iv) 5 mg/kg 9-cisRA + 200 mg/kg mitotane) for 28 days. Tumor size follow-up, histological and immunohistochemical (Ki-67) analysis, tissue gene expression microarray (4×44 K Agilent Whole Genome Microarray) have been performed. Quantitative real-time-PCR (TaqMan) was used for the validation of the microarray results and to detect circulating microRNAs.
Results
Both 9-cisRA and mitotane reduced tumor growth relative to control, but only the combination of the two agents resulted in significant tumour size reduction. The Ki-67 index was significantly reduced in both 9-cisRA and 9-cisRA + mitotane groups. Gene expression analysis revealed 483 genes with significant differences in expression, but only without Benjamini-Hochberg correction. Seven genes have been selected for validation by qRT-PCR, but only one (APOA4) was found significantly increased in the combined group compared with the control. The expression of circulating hsa-mir-483-5p was found significantly reduced in combined treatment relative to control.
Conclusions
Our results show that 9-cisRA might be a helpful additive in the treatment of ACC in combination with mitotane, but its mechanism of action awaits further investigations.

Disclosure
Hungarian Scientific Research Grant (OTKA K100295).

DOI: 10.1530/endoabs.37.GP.29.04

GP.29.05

EGFR as potential new molecular target in the medical treatment of adrenocortical cancer

Teresa Gagliano[1], Francesco Balboni[1], Carmelina Di Pasquale[1], Erica Gentilin[1], Katiusci Benfini[1], Simona Falletta[1], Marta Bondanelli[1], Paola Franceschetti[1], Carlo Feo[2], Ettore degli Uberti[1] & Maria Chiara Zatelli[1]
[1]Section of Endocrinology and Internal Medicine, Department of Medical Sciences, University of Ferrara, Ferrara, Italy; [2]Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, Ferrara, Italy.

Adrenocortical cancer (ACC) is a rare and aggressive malignancy. Currently the main therapeutic option is surgery, but due to difficult and delayed diagnosis and to the onset of metastases, medical therapy is often tried. ACC treatment is mainly represented by Mitotane alone or in association with chemotherapy, with variable results. Understanding the molecular mechanisms that regulate ACC proliferation could be useful to identify new therapeutic options. Sunitinib, a multitarget tyrosine-kinase inhibitor, showed controversial results in phase II trials for advanced refractory ACC. It has been previously demonstrated that epidermal growth factor (EGF) increases HSD3B2 expression in ACC cells. The aim of our study is to verify whether EGF pathway could represent a target for Sunitinib in human ACC cells. For this purpose we used two human adrenocortical carcinoma cell lines (SW13 and NCI-H295 cells) and human adrenal tumor primary cultures. We found that EGF increased proliferation and reduced apoptosis not only in SW13 but also in adrenal tumour primary culture, while it did not affect NCI-H295 cells. Sunitinib reduced cell viability in both cell lines, being counteracted by EGF in SW13 cells and in the majority of primary cultures analysed. We investigated in both cell lines the expression of EGFR family members, which are more expressed in SW13 cells as compared to NCI-H295 cells. Moreover, we investigated the intracellular signal transduction pathway of EGF in ACC cells. Our results show that in SW13 cells Sunitinib inhibited EGFR phosphorylation on tyrosine 1068, and counteracted EGF-induced phosphorylation of ERK1/2. In SW13 Sunitinib increased the expression of SAPK/JNK leading to caspase 3/7 activation. In NCI-H295 Sunitinib did not reduce EGFR phosphorylation, but inhibits PI3K/mTOR/AKT pathway. To verify the involvement of EGFR in regulating ACC cell viability we tested Erlotinib, a selective EGFR inhibitor, in the two cell lines. We found that Erlotinib was capable of dose dependently reducing cell viability and activating caspase 3/7 in SW13 cell line, having no effects on NCI-H295 cells. Therefore, EGF may be important in regulating EGFR expressing ACC cell proliferation. In conclusion, our data suggest that EGF pathway could represent a new molecular target in drug design for treatment of ACC that display enhanced EGFR expression.

DOI: 10.1530/endoabs.37.GP.29.05

GP.29.06

The incidence of consecutive manifestations of VHL disease

Carlijn Frantzen[1], Roeliene C Kruizinga[1], Wim J Sluiter[1], Elisabeth G E de Vries[2], Bernard A Zonnenberg[3], Cornelis J Lips[3], Annemiek M E Walenkamp[2], Anouk N A van der Horst-Schrivers[1] & Thera P Links[1]
[1]Department of Endocrinology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [2]Department of Medical Oncology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [3]Department of Internal Medicine, University Medical Center Utrecht, Utrecht, The Netherlands.

Background
Von Hippel Lindau (VHL) disease is a rare tumour syndrome with a high penetrance. VHL mutation carriers develop numerous disease related manifestations in multiple organs during life, but precise difference in growth velocity and incidence of lesions in different organs is still unknown. We aimed to gain insight in the incidence of consecutive new disease manifestations in the organs of patients with VHL.
Patients and methods
Clinical data including age at diagnosis of each new VHL-related manifestation of 75 VHL mutation carriers, with standardised follow-up, in two Dutch VHL-expert centres were retrospectively evaluated. Only consecutive lesions in the retina, the CNS, the kidneys and the pancreas were analysed. New organ lesions were defined as a new organ manifestations detected on imaging or in case of retinal lesions detected by fundoscopy. The Kaplan Meier method was used to construct the cumulative proportions of first and all consecutive manifestations in each organ against age. The cumulative average number of manifestations in all organs during life was calculated by summating these cumulative proportions. Poisson model parameters served to calculate average time to the detection of VHL manifestations in each organ.
Results
Consecutive VHL-related kidney and retina manifestations during life occur according to Poisson distribution model. The second VHL pancreas manifestation occurred later and the consecutive CNS hemangioblastomas were detected earlier than predicted by the Poisson model. The average total systemic number of manifestations rises in a linear way to seven VHL-related manifestations at age 60 years.
Conclusion
The incidence of new VHL-related manifestations after the first organ involvement is highly constant during life in VHL-carriers. Therefore, the accelerations and arrests in appearance of new manifestations observed in individual subjects are caused by the randomness of events and not by variation in disease activity.

DOI: 10.1530/endoabs.37.GP.29.06

GP.29.07

Penetrance and optimal surveillance for SDHB mutation carriers

Karin Eijkelenkamp[1], Thamara E Osinga[1], Mirjam M de Jong[2], Wim J Sluiter[1], Robin P F Dullaart[1], Thera P Links[1], Michiel N Kerstens[1] & Anouk N A van der Horst-Schrivers[1]
[1]Department of Endocrinology and Metabolic Diseases, University Medical Center Groningen, Groningen, The Netherlands; [2]Department of Clinical Genetics, University Medical Center Groningen, Groningen, The Netherlands.

Context
Germline mutations of the gene encoding succinate dehydrogenase subunit B (*SDHB*) predispose to head and neck paraganglioma (HNPGL), sympathetic PGL, phaeochromocytoma and renal cell carcinoma for which regular surveillance is required. *SDHB*-associated tumors harbor germline and somatic mutations, consistent with Knudson's two-hit hypothesis stating that the combination of an inactivating germline mutation as a first hit and somatic loss of function of the wild type allele as a second hit is essential for tumor development. The aim of this study was to assess the penetrance and optimal surveillance for different manifestations of *SDHB* mutation carriers.
Patients and methods
This study included all *SDHB* mutation carriers (18 index cases from 20 non-consanguineous families) who were prospectively followed at the department of Endocrinology at the University Medical Center of Groningen. Kaplan Meier curves were used to assess the penetrance. Poisson distribution model was used to calculate the hit rate and average time to detect the first and subsequent manifestation, to assess the optimal age to start surveillance and intervals.
Results
Eighty-three *SDHB* mutation carriers (33 men and 50 women) were included. Twenty-three mutation carriers (28%) had a manifestation, of whom 18 carriers (22%) were index patients. First manifestations included HNPGL ($n=15$), sympathetic PGL ($n=9$) and phaeochromocytoma ($n=1$), with an overall penetrance 35% at the age of 60 years. The optimal age to start surveillance for HNPGL was age 24 years, with a subsequent interval of 4 years.
Conclusion
This study emphasises a relatively low penetrance of disease in *SDHB* mutation carriers. By using a Poisson distribution model a more accurate estimation of the age to initiate surveillance and subsequent intervals is provided for HNPGL, suggesting that guideline recommendation regarding the screening of these mutation carriers might need to be revised.

DOI: 10.1530/endoabs.37.GP.29.07

Endocrine tumours and neoplasia - General

GP.30.01

Temozolomide treatment for pituitary aggressive tumours and pituitary carcinomas: initial results and long-term follow-up of a cohort of 32 cases

Hélène Lasolle[1], Fréderic Castinetti[2], Christine Cortet[3], Lucie Cloix[4], Marie Batisse-Lignier[10], Fabrice Bonnet[15], Nathalie Bourcigaux[11], Olivier Chabre[12], Philippe Chanson[17], Brigitte Delemer[6], Christine Lebrun-Frenay[7], Cyril Garcia[13], Yves Reznik[16], Franck Schillo[9], Luc Taillandier[14], Dominique Maiter[8], Jean-Louis Sadoul[7], Philipe Caron[5] & Gérald Raverot[1]
[1]Hospices civils de Lyon, Lyon, France; [2]CHU de Marseille, Hôpital de la Timone, Marseille, France; [3]CHU de Lille, Hôpital Claude Huriez, Lille, France; [4]CHU de Tours, Hôpital Bretonneau, Tours, France; [5]CHU de Toulouse, Hôpital Larrey, Toulouse, France; [6]CHU de Reims, Hôpital Robert Debré, Reims, France; [7]CHU de Nice, Hôpital de L'Archet, Nice, France; [8]Université catholique de Louvain, Clinique Universitaire Saint Luc, Bruxelles, Belgium; [9]CHU de Besançon, Hôpital Jean Minjoz, Besançon, France; [10]CHU de Clermont-Ferrand, Hôpital Gabriel-Montpied, Clermont-Ferrand, France; [11]APHP, Hôpital Saint Antoine, Paris, France; [12]CHU de Grenoble, Grenoble, France; [13]Hôpital Bégin, Paris, France; [14]CHU de Poitiers, Poitiers, France; [15]CHU de Rennes, Rennes, France; [16]CHU de Caen, Caen, France; [17]APHP, Hôpital de Bicêtre, Le Kremlin-Bicêtre, France.

Context
Successful used of temozolomide (TMZ) treatment has been described in 40–50% of aggressive pituitary tumour (PT) or rare pituitary carcinoma. These results are based on 50 case-reports and small series, data on long-term follow-up being rare.
Objectives
To describe initial results and long-term follow-up of a large French cohort of patients presenting PT treated with temozolomide.
Design
Members of the French Society of Endocrinology were surveyed regarding the clinical characteristics of PT treated with TMZ. Hormone and tumour responses to treatment were evaluated after three to six cycles and at the last follow-up.
Patients
32 patients (M=20) from 16 centers, 19 aggressive PT, 13 carcinomas including 16 ACTH, 12 PRL, and four GH-secreting tumours were followed 21.7 ± 18 months after the treatment.
Results
Age at diagnosis was 42.8 ± 19 years. All patients underwent radiotherapy, 28/32 pituitary surgeries (1–5). TMZ, 150–200 mg/m^2 5days a month, was initiated (with radiotherapy in five cases) 8.2 ± 7.5 years after diagnosis for 8.4 cycles (3–24). Tolerance was good (thrombopenia, $n=3$ and pancytopenia, $n=2$). Overall, early response was noted in 18/32 (56.3%) with similar rate between ACTH (56%) and PRL (58%), lower for GH (50%) and higher rate in adenomas (63%) than carcinomas (46%). End of treatment response was maintained in only 13/18 patients after 10.2 ± 5.6 cycles. No initial resistant cases responded to TMZ after 6.6 ± 4.4 cycles. Among the 18 responders, four were in remission (three ACTH) after 30 ± 13 months, regrowth was noted in ten patients 18 ± 18 months after TMZ administration. Second try of TMZ failed in all cases ($n=7$). 8/14 resistant cases deceased compare to 2/18 initially sensitive cases. In case of TMZ failure, carboplatin-VP16, cisplatin$\pm$adriblastine, everolimus have been tested without significant effect.
Conclusion
Initial PT response to TMZ is frequent but long-term control or remission is rare. This survey underlined lack of homogeneous therapeutic protocol and the need for guideline.

DOI: 10.1530/endoabs.37.GP.30.01

GP.30.02

Clinicopathological significance of fractional allelic loss in prognosis of follicular cell-derived thyroid tumours

Monika Migdalska-Sęk[1], Karolina H Czarnecka[1], Michał Kusiński[2], Dorota Pastuszak-Lewandoska[1], Ewa Nawrot[1], Justyna Kiszałkiewicz[1], Daria Domańska[1], Krzysztof Kuzdak[2] & Ewa Brzeziańska-Lasota[1]
[1]Department of Molecular Bases of Medicine, I Chair of Internal Medicine, Medical University of Lodz, Lodz, Poland; [2]Department of Endocrine, General and Vascular Surgery, Chair of Endocrinology, Medical University of Lodz, Lodz, Poland.

The genetic instability, i.e. loss of heterozygosity (LOH) and microsatellite instability (MSI) are frequent molecular events in thyroid tumour aetiopathogenesis. They were found in several chromosomal critical areas, including 3p12–p21.2, 3p24.2–p25.3, 7q21.1–q31.2, 10q22–24, and 15q11–q13, with loci of oncogenes and tumour suppressor genes.
Aim of the study
Evaluation of usefulness of LOH/MSI as diagnostic/prognostic biomarker in follicular cell-derived thyroid tumours.
Materials
Thyroid tumour and macroscopically unchanged tissues (control) obtained from 93 patients with: follicular adenoma (FA; $n=11$), papillary thyroid carcinoma (PTC; $n=31$), follicular thyroid carcinoma (FTC; $n=8$), and nodular goitres (NG; $n=43$).
Methods
Ten microsatellite markers linked with regions 1p31.2, 3p21.3, 3p24.2, 9p21.3, 11p15.5, and 16q22.1 were amplified in PCRs and then allelotyped. Fractional allelic loss (FAL) values defined as LOH/MSI coincidence in various chromosomal regions were assessed.
Results
LOH/MSI frequency was the highest in 3p21.3–3p24.2 (15%) and 11p15.5 (14.29%), followed by 1p31.2, 9p21.3 (12%), and 16q22.1 (10.23%). Statistical analysis of LOH/MSI frequency in FTC revealed significantly increased LOH/MSI in 1p31.2 ($P=0.028$). Significantly increased LOH/MSI in 3p21.3 was found for pT1 tumours, AJCC stage I and tumours with diameter <10 mm; in 1p31.2: for pT2–T4, stages II–IV, and tumours with diameter 10–30 mm; in 11p15.5: for pT2–T4, stages II–IV, and tumours with diameter >30 mm ($P<0.05$). Mean FAL values were significantly higher in men ($P=0.002$), and in younger patients (<40 years, $P=0.016$). FAL was significantly higher in: FA and FTC compared with NG and PTC ($P=0.033$); pT2–T4 vs pT1 ($P=0.021$). Increased FAL value significantly correlated with increased tumour diameter ($P=0.044$).
Conclusions
Our findings confirmed LOH/MSI occurrence in 3p21.3 at early stage of tumorigenesis while in 1p31.2 and 11p15.5, not recognised as critical areas, seems to be characteristic for advanced stage of thyroid tumours. FAL defined as LOH/MSI coincidence in various chromosomal regions may be useful biomarker in prediction of tumour progression. The increased FAL values in FA/FTC can be regarded as promising distinguishing biomarker from PTC and NG.
Disclosure
This work was financially supported by the Polish Ministry of Science and Higher Education (Iuventus Plus programme, 2012–2015, grant number 0082/IP1/2011/71).

DOI: 10.1530/endoabs.37.GP.30.02

GP.30.03

The role of androgen receptor in glucose transporters expression in prostate cancer cells

Pedro González-Menéndez, David Hevia, Juan C Mayo & Rosa M Sainz
Departamento de Morfología y Biología Celular, Instituto Universitario de Oncología del Principado de Asturias (IUOPA), Universidad de Oviedo, Oviedo (Asturias), Spain.

Cancer cells show different metabolic requirements than normal cells, being the high rate of glucose uptake one of the most important aspects. An increase in glucose uptake has been associated mainly with GLUT1 overexpression but may also involve other transporters including GLUT4, whose presence in prostate cancer cells was recently discovered in our laboratory. Moreover, androgens stimulate anabolic synthesis and increase glucose uptake. Despite this, the regulation of GLUT transporters by androgens has been scarcely studied. Thus, the aim of this work was to study the relation between GLUT1/4 and the androgen receptor (AR) signalling pathway in prostate cancer cells. GLUT1/4 and AR protein levels were analysed by immunoblot. Glucose uptake and glucose concentration in culture media were measured using 2-deoxyglucose and a glucometer respectively. The analysis of cell cycle was performed by flow cytometry. Finally, cell viability and proliferation were estimated by MTT reduction and Hoechst staining. Results show that GLUT1/4 expression is dependent of glucose concentration in culture media. GLUT1 was overexpressed when glucose concentration was reduced in the androgen-sensitive LNCaP and PC-3AR cells, being the number of cells in G1 phase lower. Glucose consumption was also higher in PC-3AR cells than in androgen-insensitive PC-3 cells. On the other hand, the effect of insulin (that stimulates GLUT4 transport) or indinavir (that inhibits GLUT4) were higher in androgen-insensitive cells. Moreover, AR signalling was involved in GLUT expression. Nuclear translocation of AR was increased at low glucose concentration correlating with the increment of GLUT1 levels. In addition, DHT stimulated glucose uptake and GLUT1 levels while bicalutamide (an androgen inhibitor) prevented this increment in androgen-sensitive LNCaP cells. In conclusion, AR pathway favours GLUT1 expression and functioning, while might be related to its carcinogenic properties in the prostate while GLUT4 transporter is more involved in glucose uptake in androgen-insensitive prostate cancer cells.
Disclosure
This work was supported by Ministerio de Economía y Competitivad, Gobierno de España (MINECO-13-BFU2012-38779).

DOI: 10.1530/endoabs.37.GP.30.03

GP.30.04

Re-introduction of type 1 iodothyronine deiodinase in renal cancer cells affects their migration and expression of adhesion-related genes

Piotr Poplawski[1], Joanna Boguslawska[1], Hanna Kedzierska[1], Beata Rybicka[1], Zbigniew Tanski[2], Theo J Visser[3], Alicja Nauman[1,4] & Agnieszka Piekielko-Witkowska[1]
[1]Department of Biochemistry and Molecular Biology, The Centre of Postgraduate Medical Education, Warsaw, Poland; [2]Regional Hospital Ostroleka, Ostroleka, Poland; [3]Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands; [4]Laboratory of Human Cancer Genetics, Centre of New Technologies, CENT, University of Warsaw, Warsaw, Poland.

Introduction
Type 1 iodothyronine deiodinase (DIO1) is one of the three enzymes regulating bioavailability of thyroid hormones. In contrast to DIO2 and DIO3, the specific cellular role of DIO1 remains controversial. Our previous studies showed that DIO1 expression in clear cell renal cell carcinoma (ccRCC) is decreased, followed by lowered intracellular T_3 concentration. In this study we explored how re-introduction of *DIO1* in ccRCC cells affects their migration and proliferation.
Material
75 matched pairs of ccRCC tumours and control samples, approved by the local Bioethical Committee. Two *ccRCC* cell lines *KIJ-265T* and *KIJ-308T*.
Methods
ccRCC cell lines (KIJ-265T-pcDNA3-DIO1 and KIJ-308T-pcDNA3-DIO1) with stable re-expression of DIO1 and control cell lines (KIJ-265T-pcDNA3 and KIJ-308T-pcDNA3) stably transfected with empty pcDNA3 vector were generated. The expression of genes involved in adhesion and ECM was analysed with RT^2 Profiler PCR Array (SABiosciences), followed by SYBRGreen/qPCR validation. Scratch test and Cell Proliferation ELISA, BrdU were used for analysis of migration and proliferation respectively.
Results/conclusions
Expression of collagen COL1A1 and integrin ITGB2 was elevated in ccRCC tumours compared with control samples. Re-expression of DIO1 in KIJ-265T (grade IV) and KIJ-308T (grade II) cell lines resulted in decreased expression of COL1A1 (74 and 68% respectively) and ITGB2 (58 and 34% respectively). Scratch test revealed that migration of KIJ265 was stimulated by DIO1 expression while in KIJ308T DIO1 had no effect. Proliferation of both cells was reduced by DIO1 expression. We show, for the first time, that DIO1 has opposite roles in ccRCC tumourigenesis: it reduces proliferation with concomitant stimulation of migration in higher tumour grade cells. This effect is probably mediated by DIO1-induced changes in expression of genes involved in cellular adhesion. The specific mechanisms of DIO1 action in ccRCC require further investigation.
Disclosure
This work was supported by National Science Centre grants: 2012/05/B/NZ5/01541 (A Piekielko-Witkowska) and NN401611940 (A Nauman).

DOI: 10.1530/endoabs.37.GP.30.04

GP.30.05

Targeted destruction of FSHR-positive cells by lytic peptide Phor21 conjugated with FSHβ subunit *in vitro*

Marcin Chrusciel[1,2], Joanna Stelmaszewska[3], Donata Ponikwicka-Tyszko[2], Milena Doroszko[1], Slawomir Wolczynski[2,3], Ilpo Huhtaniemi[1,4], Adam Ziecik[2] & Nafis Rahman[1,3]
[1]Department of Physiology, Institute of Biomedicine, University of Turku, Turku, Finland; [2]Institute of Animal Reproduction and Food Research, Polish Academy of Sciences, Olsztyn, Poland; [3]Department of Reproduction and Gynecological Endocrinology, Medical University of Bialystok, Bialystok, Poland; [4]Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, London, UK.

FSH receptor (FSHR) expression has been shown in gonadal tumours, as well as in endothelial tumour vessel cells of various cancers. FSHR, due to its transmembrane localization could be a good candidate for receptor-mediated targeted cancer therapy. In recent years, a number of membrane disrupting lytic peptides have been used for receptor-based cancer therapy. In the present study, we characterised the specificity and cytotoxicity of a lytic peptide Phor21 conjugated to three different amino-acid (AA) sequence fragments of the FSHβ-chain (AA33–53, AA81–95, and AA33–53 + 81–95) with several other enhancing modifications of the peptides, to ablate FSHR-positive cells *in vitro*. As there exists no cancer cell lines expressing functional endogenous FSHR, Phor21-FSHβ conjugates were tested in a human FSHR cDNA-stably transfected HEK293 cell line (FSHR-positive cell) and HEK293 (FSHR-negative cells). Conjugate-mediated cytotoxicity was assessed by measurement of lactate dehydrogenase (LDH), a stable cytosolic enzyme that is released upon membrane disruption by lytic peptide. Conjugate of Phor21 linked to FSHβ–AA33–53, in which cysteine (Cys53) was replaced by serine (Ser) and stabilized with N-terminal amino group (Phor21-FSHβ33–53Cys/Ser-CONH) displayed the highest specific cytotoxicity to FSHR-positive cells vs. any other tested compound. Phor21-FSHβ33–53Cys/Ser-CONH conjugate showed in a dose dependent manner (0.5, 1, 2.5, and 5 μM) two- to ten fold higher ability to destroy the FSHR-positive cells than Phor21 alone. Pre-incubation or co-treatment competitive studies in FSHR-positive cells with recombinant human FSH 100 IU/L significantly decreased the cytotoxicity of Phor21-FSHβ33–53C/S-CONH conjugate at two lowest concentrations (0.25 and 0.5 μM). Conjugating FSHβ fragment sequences to Phor21 slightly enhanced their cytotoxic effects in comparison to Phor21 backbone in FSHR-negative cells. Our results prove the principle that Phor21-FSHβ33–53Cys/Ser-CONH may provide a novel specific therapeutic lead into targeted destruction of FSHR expressing cancer cells *in vitro* and as well as for further *in vivo* studies.

Disclosure
Polish National Science Centre (2012/05/B/NZ5/01867), Academy of Finland.
DOI: 10.1530/endoabs.37.GP.30.05

GP.30.06

The Wnt/β-catenin pathway regulates the expression of early embryonic stem cell genes in human parathyroid tumours

Chiara Verdelli[1], Irene Forno[2], Valentina Vaira[2,3], Vito Guarnieri[4], Alfredo Scillitani[5], Filomena Cetani[6], Leonardo Vicentini[7], Gianni Balza[8], Edoardo Beretta[9] & Sabrina Corbetta[10]
[1]Laboratory of Molecular Biology, IRCCS Policlinico San Donato, San Donato Milanese (MI), Italy; [2]Division of Pathology, IRCCS Fondazione Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; [3]Istituto Nazionale Genetica Molecolare (INGM) Romeo ed Enrica Invernizzi, Milan, Italy; [4]Medical Genetics, IRCCS Hospital Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy; [5]Endocrinology Unit, IRCCS Hospital Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy; [6]Endocrine Unit 2, Department of Clinical and Experimental Medicine, University of Pisa, University Hospital of Pisa, Pisa, Italy; [7]Endocrine Surgery, IRCCS Fondazione Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; [8]General Medicine Unit, AO Alessandro Manzoni, Lecco, Italy; [9]Endocrine Surgery, IRCCS Ospedale San Raffaele, Milan, Italy; [10]Endocrinology and Diabetology Unit, Department of Biomedical Sciences for Health, IRCCS Policlinico San Donato, University of Milan, San Donato Milanese (MI), Italy.

Though there is no evidence of a constitutive nuclear accumulation of β-catenin, the Wnt/β-catenin pathway might be deregulated in parathyroid tumours. We investigated unphosphorylated active β-catenin distribution by western blot in 16 typical parathyroid adenomas (PAds): β-catenin accumulation in the nuclear protein fractions varied from the levels detected in Caco-2 cells with constitutively active Wnt signalling (three PAds) to the levels measured in HEK293 cells with intact Wnt signalling (six PAds) and positively correlated with *AXIN2* mRNA levels ($r = 0.546$, $P = 0.03$). The Wnt/β-catenin pathway is intimately connected to the embryonic pluripotent core circuitry. Therefore, we treated PAds-derived cells ($n = 3$) with 10–20 mM lithium chloride for 72 h: we detected nuclear accumulation of β-catenin and concomitant increases in mRNA levels of *NANOG*, decreases of *SOX2*, no changes of *POU5F1/OCT4*. In PAds nuclear β-catenin levels positively correlated with the *NANOG* mRNA levels and negatively with the *SOX2* mRNA levels. Immunohistochemistry of tumour sections (11 PAds and eight carcinomas (PCas)) identified cells expressing at nuclear level the stem cell genes: NANOG-expressing cells were more abundant in parathyroid carcinomas (40.0 ± 5.8%; range 30–70%) than in PAds (11.4 ± 4.5%; range 1–40%; $P = 0.01$), while OCT4 was similarly detected in 5–20% of cells in both PAds and PCas and 42% of PAds showed SOX2-expressing cells. SOX2-expressing cells were more abundant in PAds than in PCas (15.8 ± 5.9% vs 7.0 ± 3.6%; $P = 0.05$). Patients harbouring the PAds with detectable *SOX2* transcripts ($n = 22$) had a more severe hyperparathyroidism at diagnosis: serum PTH and calcium levels were higher than that in patients with *SOX2*-undetectable PAds ($n = 14$; PTH: 324.2 ± 248.0 pg/ml vs 150.2 ± 56.0 pg/ml; $P = 0.014$; calcium: 11.9 ± 1.2 mg/dl vs 11.2 ± 0.7 mg/dl, $P = 0.06$). Immunofluorescence detected few cells coexpressing SOX2 and NANOG or OCT4, while parathyroid tumour cells expressing PTH were negative for all the stem cell genes. In conclusion, we firstly showed that i) a subset of parathyroid tumour cells express the pluripotent stem cell genes and ii) β-catenin might be involved in the regulation of the stem-like phenotype acquisition by a subset of parathyroid tumour cells.

Disclosure
This work was supported by the IRCCS Policlinico San Donato Research Found.
DOI: 10.1530/endoabs.37.GP.30.06

GP.30.07

Steroid metabolome analysis reveals that prostate cancer has potent 5α-reductase, 3α- and 17β-hydroxysteroid dehydrogenase activities, but lacks 17-hydroxylase/17,20-lyase

Johannes Hofland[1,2], Angela E Taylor[1], Orli Turgeman[1], Donna M O'Neil[1], Paul A Foster[1] & Wiebke Arlt[1]
[1]Centre for Endocrinology, Diabetes and Metabolism, University of Birmingham, Birmingham, UK; [2]Erasmus MC, Rotterdam, The Netherlands.

Introduction
Prostate cancer (PC) is dependent on androgen receptor (AR) activation by its canonical ligands testosterone and 5α-dihydrotestosterone (DHT). Intratumoural androgens persisting after castration give rise to castration-resistant PC (CRPC). These intraprostatic androgen levels are hypothesized to result from either adrenal androgen conversion or intratumoural *de novo* DHT synthesis through the classic or alternative pathways. Quantifying the steroid fluxes responsible for CRPC development can help optimize current endocrine treatment strategies.
Methods
Five PC cell lines were incubated with 1 μM of 16 steroid intermediates of the classic and alternative androgen synthesis pathways. A PC steroid metabolome was constructed through measurement of steroid metabolite concentrations with liquid chromatography/tandem mass spectrometry (LC–MS/MS). Steroidogenic enzyme expression was estimated by quantitative PCR.
Results
Steroid metabolites could be detected for up to three enzymatic steps downstream of the employed steroid substrate. 17-hydroxylase/17,20-lyase activity was undetectable in all PC cell lines with eight different substrates tested, thereby excluding conversion above 0.03% of the substrate. In contrast, 3α-, 3β- and 17β-hydroxysteroid dehydrogenase and 5α-reductase activities were present in all cell lines to varying degrees. Steroid flux analysis confirmed conversion of adrenal androgen precursors and androgen metabolites into DHT. Furthermore, C21 steroids progesterone and 17hydroxy-progesterone were metabolised into intermediates of the alternative pathway without reaching androsterone. The highest steroidogenic activity was observed in C4-2B cells, a castration-resistant, bone-metastasizing clone of LNCaP. Expression profiles of steroidogenic enzymes matched the observed enzymatic activities.
Conclusion
For the first time, a quantitative steroid metabolome of PC cells has been generated through LC–MS/MS, providing strong evidence against intratumoural *de novo* steroid synthesis. Adrenal androgens can effectively be converted into DHT, whereas precursor C21 steroids divert towards the alternative pathway. The presence of these hormones in PC might suggest a role for activity or further metabolism of alternative pathway steroids in PC evolution.

Disclosure
This work was supported by the European Union (Marie-Curie Intra-European Fellowship, grant number PIEF-GA-2013-629745).
DOI: 10.1530/endoabs.37.GP.30.07

E-Posters

Adrenal cortex

EP1

Evaluation of cases by short synacthen test (dose: 250 μg i.v.) suspected as secondary adrenal insufficiency of prolonged steroid abuse

S M Ashrafuzzaman, Jubaidul Islam & Zafar A Latif
BIRDEM, DHAKA, Bangladesh.

Introduction
Adrenal insufficiency is a common problem in our country due to steroid abuse in various forms. In many occasions the patients even do not know about its side effects and consequences of non-prescribed usage. Many of them presents with sudden withdrawal and adrenal crisis. Many of them admits in Gastroenterology unit due to vomiting, some of them in Medical unit with unexplained fever, weakness, anaemia, etc. Many of them having subtle features of Iatrogenic Cushing's. In this case series, patients of history of chronic steroid use but, are not taking steroid at least since last 4 weeks are evaluated due to their minimal symptoms.
Methods
All patients having history of supraphysiological dose of steroid use more than 3 months in any form but not taking for at least 1 month. Clinically stable, not at crisis. All 34 subjects were evaluated by short synacthen test 250 μg i.v. Three samples S.cortisol were test 0 h, and after Inj. synacthen 250 μg i.v. 30 and 60 min. S.ACTH was tested with 0 min cortisol.
Result
At 0 h S.cortisol value ranges from 53 to 313 nmol/l. At 30 min after Inj. synacthen 250 μg i.v. S.cortisol ranges from 76 to 622 nmol/l and at 60 min 87–587 nmol/l. In the group who has 0900 h S.cortisol <140 nmol/l ($n=15$) they have at 30 min S.cortisol 53–411 nmol/l and at 60 min 76–527 nmol/l. S.ACTH at 0900 h was within normal limit.
Conclusion
In cases of suspected secondary adrenal insufficiency due to steroid abuse (basal S.cortisol <240 nmol/l) synacthen test with 250 μg Tetracosactren (Synacthen) i.v. mostly shows partial adrenal insufficiency. In most cases immediate replacements were depended on clinical presentation not on lab values. So for representative lab values (whom to treat or not to treat with steroid) dose of synnacthen for the 'TEST' can be reconsidered at lower dose between 1 and 250 μg. As 1 μg is not available, preparation by self-dilution method, is not standardised in lab always. Pharmaceutical companies should be requested for standard strength of ACTH may be 10–100 μg/ml for dispensing. Further RCT with 1 μg to 10 μg can be considered to find the standard dose of the 'Low Dose Test'.

DOI: 10.1530/endoabs.37.EP1

EP2

Management of urgent surgical intervention due to coexistence of phaeochromocytoma and hydrocephalus in a patient presenting with Von Hippel Lindau syndrome

Gulsah Yalin[1], Mehmet Barbur[2], Gulcin Yegen[3], Seher Tanrikulu[1], Ayse Kubat Uzum[1], Ferihan Aral[1] & Refik Tanakol[1]
[1]Division of Endocrinology, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey; [2]Division of Radiology, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey; [3]Division of Pathology, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey.

A 41-year-old woman was admitted with headache and hypertension. She described worsening of headaches in the last 2 months. On physical examination blood pressure was 150/90 mmHg, and grade 1 hypertensive retinopathy was present. Her sister died at the age of 24 due to pancreas neuroendocrine tumour and her mother was followed up with multiple pancreatic cysts. Abdomen MRI revealed a 6 cm phaeochromocytoma lesion on the right surrenal and multiple cysts in the pancreas, kidneys and ovaries. Urinary catecholamin levels were elevated by sixfold. Other laboratory results were normal. Doxazosin 4 mg (b.i.d.) and amlodipin 5 mg were initiated. Patient's family history, presence of multiple visceral cysts and phaeochromocytoma led us to consider Von Hippel Lyndau sydrome. Cranium MRI which was performed due to severe headaches revealed a 5 cm serebellar hemanjioblastoma and hydrocephalus of the third ventricle. Urgent surgical intervention was indicated due to presence of hydrocephalus and risk of herniation. Coexistence of phaeochromocytoma, risk of hypertensive crisis and deterioration of herniation with anaesthesia induction made it mandatory to perform the two surgeries sequentially in the same surgical session. As the patient had been receiving α blockers for a sufficient time of preoperative period, laparoscopic right surrenalectomy was performed, followed by hemangioblastoma excision in the same session. Pathological evaluation revealed, right surrenal phaeochromocytoma with a Ki score of 3% and grade 1 serebellar hemanjioblastoma. Two months after the surgery patient was normotensive without any antihypertensive treatment and symptoms of headache were omitted. Screening of the family members revealed multiple pancreas, renal and epididymal cysts, serebellar hemangioblastoma and phaeochromocytoma in her brother compatible with Von Hippel Lindau syndrome and treatment was initiated. Evaluation of the other family members were normal and a surveillance programme was scheduled.
Conclusion
Hemangioblastoma of central nervous system which may complicate the surgery of phaeochromocytoma must be considered in patients who present with phaeochromocytoma and multisystemic manifestations implicating presence of a genetic syndrome.

DOI: 10.1530/endoabs.37.EP2

EP3

A case of polyglandular autoimmune syndrome type 1 with hypercalcaemia and hypotension

Nilufer Ozdemir Kutbay[1], Banu Sarer Yurekli[1], Miray Yaman[2], Mehmet Erdogan[1], Sevki Cetinkalp[1], Fusun Saygili[1], Sukran Darcan[3] & Gokhan Ozgen[1]
[1]Endocrinology and Metabolism Department, Faculty of Medicine, EGE University, Izmir, Turkey; [2]Internal Medicine Department, Faculty of Medicine, EGE University, Izmir, Turkey; [3]Pediatric Endocrinology and Metabolism Department, Faculty of Medicine, EGE University, Izmir, Turkey.

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is also known as autoimmune polyendocrine syndrome type 1 (APS-1). We present a case of autoimmune polyendocrine syndrome type 1 with hypercalcaemia of adrenal insufficiency during the calcium treatment because of hypoparathyroidism.
Case
A 20-year-old female patient was diagnosed with APS-1 in 2004. She applied to ER with the complaints of nausea and vomiting. Her laboratory findings proved hypercalcaemia, hyponatremia and hypotension. She'd had an upper respiratory infection a week prior to her application to our hospital. In her ECG, t-waves were found to be commonly inverted. Her echocardiography revealed increased pericardial brightness. Thus, indomethacin 2×1 was started as pericardite was suspected. BP of 90/40 mmHg and dry skin were found in the physical examination. Horizontal ridges and trophic deformities on both finger nails and toes were observed (Picture 1). The laboratory findings were as follows: BUN: 58 mg/dl, creatinine: 0.82 mg/dl, Na: 127 mEq/l, K: 4.6 mEq/l, Ca: 12.6 mg/dl, FSH: 4.42 mIU/ml, LH: 5.63 mIU/ml, ACTH: 124 pg/ml, cortizol: 0.40 μg/dl, DHEAS: 4.6 μg/dl, free T_3: 1.94 pg/ml, free T_4: 1.07 ng/dl, TSH: 3.26 μIU/ml, anti TPO: 14.7, PTH: 0.01 pg/ml. Hypercalcemia was associated to adrenal insufficiency. I.v. hydration and steroid of stress dose was started because of hypercalcemia and hypotension. We applied maintenance doses of hydrocortisone (30 mg/day) and fludrocortisone ($0.1\text{ mg}\times1/2$ a day) to the improved patient. Calcitriol and calcium were restarted to the patient as her Ca level was 6.5 mg/dl in the follow-up period. The patient had a leukoplakic lesion characterized with candida plaque on the right buccal mucosa. Thus, sodium bicarbonate and mycostatin suspensions were added to the treatment.
Discussion
The most important components of OPS type 1 are hypoparathyroidism, Addison's disease and candidiasis with other disease associations of hypothyroidism, hypogonadism and infertility, alopecia (baldness), malabsorption, chronic active (autoimmune) hepatitis. It is a genetic disorder inherited in autosomal recessive tendency due to a defect in the auto immune regulator (AIRE) gene located on chromosome 21.q223. In our case, hypercalcaemia was thought to develop as a result of calcitriol and calcium treatment and addition of adrenal insufficiency. One should always remember that calcitriol and calcium treatment simultaneously with adrenal crisis triggered by stress assist the development of hypercalcaemia in the cases with APECED.

DOI: 10.1530/endoabs.37.EP3

EP4

The value of high effective liquid chromatography in the diagnosis of primary aldosteronism

Dina Rebrova, Natalya Vorokhobina, Ludmila Velikanova & Zulfiya Shafigullina
North-Western State Medical University n.a. I.I. Mechnikov, St. Petersburg, Russia.

Objectives
Primary aldosteronism (PA) is considered to be the most common cause of secondary hypertension. Therefore, a relevance of early diagnosis of PA is obvious.
Methods
We evaluated 98 patients with hypertension in age 47.8 ± 1.4 years. We measured serum potassium by indirect porentiometry, serum aldosterone and plasma rennin activity (PRA) by RIA, serum corticosterone (B), 18-hydroxycorticosterone (18-OH-B), 11-deoxycorticosterone (DOC), 11-dehydrocorticosterone (A), 11-deoxycortisol (S) and urine 18-hydroxycorticosterone (U18-OH-B) by high effective liquid chromatography (HELC). All patients underwent saline infusin test and computed tomography with contrast. Adrenal vein sampling (AVS) was performed in all patients with confirmed PA.
Results
PA was diagnosed in 46 patients, 27 of them had unilateral form – aldosterone-producing adenoma (APA), 19 – idiopathic hyperplasia (IHA). 52 patients were found essential hypertensives (EH), 27 of them were low-renin EH. PA patients had higher levels of some corticosteroids than EH: B (6.5 ± 0.8 vs 3.0 ± 0.6 ng/ml respectively, $P < 0.001$), DOC (7.8 ± 1.4 vs 2.0 ± 1.8 ng/ml respectively, $P < 0.01$), 18-OH-B (2.1 ± 0.5 vs 4.8 ± 0.5 ng/ml respectively, $P < 0.001$), S (4.4 ± 1.2 vs 1.0 ± 0.3 ng/ml respectively, $P < 0.01$), A (6.4 ± 0.8 vs 2.5 ± 0.3 ng/ml respectively, $P < 0.001$).
Conclusion
The determination of the precursors of aldosterone in blood and urine samples by HELC is a safe method for the patients who have contraindications to recommended confirmatory tests. It can be used in patients with uncontrolled hypertension and high risk of cardiovascular complications. Our data showed that increased levels of serum B, S, DOC, A and 18-OH-B, U18-OH-B are laboratory signs of PA which can be determined during screening.

DOI: 10.1530/endoabs.37.EP4

EP5

Influence of glucocorticoids on markers of inflammation in community-acquired pneumonia

Claudine A Blum[1,2], Nicole Nigro[1], Philipp Schuetz[3], Bettina Winzeler[1], Birsen Arici[1], Julie Refardt[1], Sandrine A Urwyler[1], Matthias Briel[1,4], Beat Mueller[3] & Mirjam Christ-Crain[1]
[1]Endocrinology, Diabetology and Metabolism, Department of Internal Medicine and Department of Clinical Research, University Hospital Basel, Basel, Switzerland; [2]Service d'Accueil des Urgences, CHU Pitié-Salpêtrière et AP-HP, Paris, France; [3]Medical University Clinic, Departments of Internal and Emergency Medicine and Department of Endocrinology, Diabetology and Clinical Nutrition, Kantonsspital Aarau, Aarau, Switzerland; [4]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada.

Background
Glucocorticoids are frequently prescribed in inflammatory diseases. We investigated the influence of prednisone on classical and novel inflammatory markers in community-acquired pneumonia (CAP).
Methods
We evaluated levels of C-reactive protein (CRP), procalcitonin, leukocyte and neutrophil count in a prospective randomized, double-blind, placebo-controlled multicenter trial which compared prednisone 50 mg for 7 days to placebo in patients hospitalized with CAP. We performed Mann–Whitney *U* tests to compare biomarker levels between groups on day 1 before the first administration of prednisone and thereafter on days 3, 5, 7 and discharge.
Results
335 patients in the prednisone group and 350 patients in the placebo group were evaluated. At baseline, all investigated markers levels did not differ between prednisone and placebo group. At days 3, 5, and 7, CRP levels were significantly lower in the prednisone group than in the placebo group ($P < 0.0001$ for each time point). At hospital discharge, CRP levels were similar ($P = 0.53$). For procalcitonin, this attenuating effect of steroids on circulating levels was not visible ($P > 0.05$ for all points). Leukocyte and neutrophil count were higher in the prednisone group during administration of glucocorticoids ($P < 0.0001$ for all time points including discharge).
Discussion
Administration of glucocorticoids in patients with CAP lowers CRP levels and increases leukocyte and neutrophil count, but has no influence on procalcitonin levels. Therefore, procalcitonin may be a more adequate inflammatory marker to measure treatment response in patients with an infectious disease receiving glucocorticoids.

Disclosure
This work was supported by the Swiss National Science Foundation (grant numbers PP0P3_123346, P2BSP3_155212, PP00P3_150531/1, 320030-138267, and 320030-150025), the Nora van Meeuwen Häfliger Stiftung, the Gottfried Julia Bangerter-Rhyner Stift.

DOI: 10.1530/endoabs.37.EP5

EP6

Clinical and pathological characteristics of hypertensive and normotensive adrenal phaeochromocytomas

Bi Yan, Zhu Dalong & Lu Yao
Drum Tower Hospital Affiliated to Nanjing University Medical School, Nanjing, China.

Context
Distinct differences of clinical manifestations exist in hypertensive pheochromocytomas (HPs) and normotensive phaeochromocytomas (NPs), however the comparative analysis is lacking.
Objective
The objective of the study was to assess the clinical symptoms, haemodynamics, metabolism, radiological and histological features of patients with HPs and NPs.
Research design and methods
This retrospective study included 104 patients who underwent a unilateral adrenalectomy with a diagnosis of phaeochromocytoma at the Drum Tower Hospital Affiliated to Nanjing University Medical School from January 2004 to December 2014. All available clinical, biochemical, and radiological records were reviewed in phaeochromocytomas patients who were then categorized into HPs ($n = 69$) and NPs ($n = 35$) groups. Tumour samples were examined to determine the adrenal gland scale score and were available for measurement of gene transcriptions. Clinical and biochemical examinations of consecutive 95 subjects with primary hypertention (PH) were recorded for comparative study.
Results
Patients with NPs showed lower proportion of clinical triad, inapparent metabolic disorders and lower urinary catecholamine levels than HPs, but higher than PH. Tumour weight positively correlated with 24 h urinary norepinephrine level in patients with HPs ($P = 0.028$), and tumour diameter negatively correlated with phenylethanolamine-*N*-methyltransferase (PNMT) immunohistochemistry ($P = 0.011$) in NPs but not in HPs. The adrenal gland scale score of NPs group was similar to that of HPs group. The positive percentage of E-type of catecholamine in HPs group was higher than that in the NPs, while the positive percentage of NE-type or no function of catecholamine in HPs group was lower than that of the NPs. The transcript levels of PNMT, secretogranin II (SGII) and neuropetide Y (NPY) from tissue samples were significantly lower in NPs than in HPs, while vesicular monoamine trasporter 1 (VMAT1) had no difference between HPs and NPs.
Conclusions
HPs and NPs have distinct differences in clinical, biochemical and pathological phenotypes, which are closely related with the catecholamine pathway productions involved in tumour occurrence and development.

DOI: 10.1530/endoabs.37.EP6

EP7

New onset sarcoidosis after remission of Cushing's syndrome

Zeynep Canturk[1], Alev Selek[1], Serap Bariş[2], Berrin Cetinarslan[1], Ilhan Tarkun[1] & Zeynep Akyay[1]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Kocaeli University, Kocaeli, Turkey; [2]Department of Chest Diseases, Faculty of Medicine, Kocaeli University, Kocaei, Turkey.

Introduction
Glucocorticoids, even endogenous or exogenous, suppress the inflammatory response therefore they are the most preferred treatment options in inflammatory diseases. Persistent hypercortisolism induces lymphopenia and lymphoid tissue atrophy. Excessive endogenous hypercortisolism might mask the active inflammatory disease. Rebound immune modulation may occur after Cushing's syndrome (CS) remission, leading to the new onset of autoimmune diseases.
Case
Here, we report a 27-year-old female patient newly diagnosed as sarcoidosis after remission of CS. Adrenal CS was treated successfully with right adrenalectomy. The patient was free of sarcoidosis during the course of CS with normal thorax imaging and without any symptoms of sarcoidosis. After complete remission of

CS she started to complain of cough and was diagnosed sarcoidosis with clinical, radiological and bronchoscopic evidence.
Conclusion
Endogenous Cushing's syndrome is caused either by excess ACTH secretion or by autonomous cortisol release from the adrenal cortex. Glucocorticoids are the main endogenous mechanism to suppress the inflammatory response genes. Exposure to persistent hypercortisolism induces lymphopenia and lymphoid tissue atrophy resulting in immunosupression. After treatment of CS rebound immunity occurs especially in patients with overt disease. In rare cases, the treatment of CS may result in unmasking or aggravation of diseases responsive to glucocorticoid medication such as thyroid, rheumatologic and allergic diseases. Excessive hypercortisolism might suppress the active inflammatory stage of sarcoidosis. However, the disease became apparent after the reduction of cortisol levels following the treatment of CS.

DOI: 10.1530/endoabs.37.EP7

EP8

Extra-adrenal myelolipomas in association with cortisol hypersecretion

Betul Cavusoglu[2], Evrim Cakir[1], Suleyman Ahbab[2], Esra Ataoglu[2] & Mustafa Yenigun[2]
[1]Haseki Training and Research Hospital, Endocrinology and Metabolic Diseases, Istanbul, Turkey; [2]Haseki Training and Research Hospital, Internal Medicine, Istanbul, Turkey.

Extraadrenal perirenal myelolipom has been reported since 1980. In recent years, it has been reported at an increasing rate in different sites of the body ranging from the nasal cavity, mediastinum to presacral, paravesical region. However, it was the first reported case that perirenal multiple myelolipomas, each myelolipomas was about 5 cm in diameter, in associated with cortisol hypersecretion. A patient was an emigrant. She was followed in her country and was prescribed ketokonazol. She did not take her medicine and she was brought to emergency service when her situation deteriorated. She was exposed to hypercortisolemia for a long time and had severe muscle weakness, fatigue, amenorrhea and weight loss at admitted-time. Physical examination revealed cushingoid appearance with trunk obesity, sebaceous moon face, hirsutism, muscle wasting, high blood pressure, acanthosis nigricans and abdominal striae. Laboratory tests were as following; glucose: 170 mg/dl (70–100), urea:42.3 mg/dl (17–43), creatinin: 0.82 mg/dl (0.51–0.95), sedimentation: 35 mm/h (0–30), HbA1c: 8.8%, FSH: 1.59 mIU/ml (4.54–22.51) LH: 0.31 mIU/ml (12–12.86 mIU/ml), estradiol: 16 pg/ml (49–291), progesterone: 1.75 ng/ml (5.16–18.56), total testesterone: 0.48 pg/ml (0.1–0.75), cortisol: 30.40 μg/dl (6.7–22.6), ACTH: <1 pg/ml (7.2–63.3). Eosinopenia, lymphocytopenia and neutrophilia was obtained in whole blood cell evaluation. Cortisol level was 27.60 μg/dl after 1 mg dexamethasone suppression test, result revealed failure of suppression. Pituitary MR was normal. A contrast enhanced abdominal MR showed multipl lobulated bilateral perirenal masses and a cystic mass at the caput of the pancreas without solid component. Majority of perirenal masses was located in the right perirenal area with 5×4 cm in diameter. The MR followed by a F-18 fluorodeoxyglucose tomography (FDG PET/CT). The increased FDG uptake in the right pararenal area. Myelolipoma was diagnosed in microfiber biopsy of the perirenal mass. In her hospitalisation period femur fracture occurred. After operation for femur fracture she could not be extubed because of the respiratory muscle weakness. Adrenal myelolipomas with Cushing syndrome have been reported previously. However, extra-adrenal perirenal myelolipomas presented with Cushing syndrome is the first case of the literature.

DOI: 10.1530/endoabs.37.EP8

EP9

Salivary cortisol after overnight dexamethasone suppression test in different patient groups

Meral Mert[1], Refik Tanakol[2], Hande Karpuzoglu[3], Semra Dogru Abbasoglu[3], Ozlem Soyluk[2], Sema Yarman[2] & Faruk Alagol[2]
[1]Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Endocrinology and Metabolism, Istanbul, Turkey; [2]Division of Endocrinology and Metabolism, Department of Internal Medicine, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey; [3]Department of Biochemistry, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey.

Introduction
The aim of this study was to evaluate the worth of the salivary cortisol after overnight 1 mg dexamethasone suppression test (DST) in different patients.
Materials and methods
The patient groups of the study consisted of 18 Cushing's syndrome patients, 12 patients with non-functional adrenal incidentaloma, 37 patients with obesity, 16 patients with hirsutism and 26 healthy control patients. Salivary cortisol (SC) and plasma cortisol after 1 mg-overnight DST were measured. SC was measured with luminescense immunoassay kit.
Results
Salivary cortisol levels after overnight DST was found significantly different between all groups ($P<0.05$) except between patients with hirsutism and obesity and between patients with adrenal incidentaloma and healthy control group ($P=0.357$). In this context, plasma cortisol levels after overnight DST were not significantly different between patients with hirsutism and control group and between patients with obesity and control patients both, while it was significantly different between all the other groups.
When all the patient groups are evaluated in a whole group there was a significant positive correlation between plasma and salivary cortisol ($r=0.542$, $P=0.0001$). In the subgroup analyses, there was no correlation between salivary and plasma cortisol in patients with hirsutism and Cushing's syndrome. In the groups with adrenal incidentaloma and healthy control, highly significant correlation between salivary and plasma cortisol was found ($r=0.750$ – $P=0.02$, $r=0.679$ – $P=0.008$ respectively).
Conclusion
Salivary cortisol after overnight DST may be one of the new non-invasive diagnostic tools for the differential diagnosis of Cushing's syndrome and pseudo-Cushing syndrome. However, laboratory test results and clinical findings should be evaluated together in clinical practice.

DOI: 10.1530/endoabs.37.EP9

EP10

Overview of phaeochromocytomas at Vilnius University Hospital Santariskiu clinics (VUHSC): 5 year results

Milda Girdziute[1] & Zydrune Visockiene[1,2]
[1]Vilnius University, Vilnius, Lithuania; [2]Vilnius University Hospital Santariskiu Clinics, Vilnius, Lithuania.

The aim of our study was to estimate the prevalence and describe diagnosis, treatment and follow up strategy of phaeochromocytomas at VUHSC.
Results
There were 702 patients diagnosed with adrenal masses from 2010 to 2014. Only half of patients were screened for phaeochromocytoma which included 24 (the incidence is 3.4%). Phaeochromocytoma was diagnosed in 5 (20.8%) males and 19 (79.2%) females, average age 55 ± 11.5 years. After surgery 2 (8.3%) were confirmed as paragangliomas. Although there were 21 (87.5%) symptomatic patient – most commonly with hypertension – 16 (66.7%), episodic tachycardia – 13 (54.2%), episodic elevations of blood pressure – 12 (50.0%) and sweating – 4 (16.7%), phaeochromocytoma was found incidentally in 15 (62.5%) cases. The average tumour size of 48.0 ± 23.4 mm and density of 33.7 ± 11.6 HV was estimated by computed tomography performed for all patients. Most tumours were found in the left adrenal – 15 (62.5%), bilaterally – in 1 (4.2%) patient. In 45.8% of cases scintigraphy with iodine-123-metaiodobenzylguanidine was performed and uptake confirmed in all suspected tumours. Hormonal activity was confirmed in 20 (83.3%) cases by elevation of plasma metanephrine and/or normetanephrine or urine/plasma adrenaline and/or noradrenaline. Isolated elevations of either adrenaline or metanephrine was detected in 4 (16.7%), noradrenaline or normetanephrine – in 3 (12.5%) cases. Adrenalectomy was performed in 21 (87.5%) patient with suspicion of malignant tumour in 9 (42.9%) of cases after histological examination. Two of them received chemotherapy, but were diagnosed with the recurrence of disease, others are under follow up with no disease relapse. Genetic syndromes were diagnosed in 2 (8.3%) subjects: Von Hippel Lindau syndrome and type 1 neurofibromatosis.
Conclusions
The incidence of phaeochromocytoma in our hospital is 3.4% and meets the rates estimated by others. High prevalence of asymptomatic patients and suspicion of malignant tumours after histology urge for careful assessment of all adrenal masses for phaeochromocytoma.

DOI: 10.1530/endoabs.37.EP10

EP11

Aldosterone- and cortisol-co-secreting adrenal adenoma in an adolescent girl: a case report

Serap Baydur Sahin[1], Ahmet Hamdi Aktan[2], Osman Zikrullah Sahin[3], Ahmet Fikret Yucel[4] & Ekrem Algun[1]
[1]Department of Endocrinology and Metabolism Disease, Recep Tayyip Erdogan University Medical School, Rize, Turkey; [2]Department of Internal Medicine, Recep Tayyip Erdogan University Medical School, Rize, Turkey; [3]Department of Nephrology, Recep Tayyip Erdogan University, Rize, Turkey; [4]Department of General Surgery, Recep Tayyip Erdogan University, Rize, Turkey.

Introduction
Primary aldosteronism (PA) is the most common reason for secondary hypertension. Among adrenal disorders, rarely aldosterone- and cortisol-co-secreting adenomas (A/CPA) can lead to PA. 35 patients with A/CPA were reported to date and their mean age was 52 (range 34–80) years. We report an A/CPA in an adolescent girl presenting with hypertension combined with hypokalemia and signs of hypercortisolism.
Case report
A 18-year-old girl admitted to endocrinology outpatient clinic with the complaint of hypertension. Physical examination revealed central obesity (BMI:31 kg/m^2), moon face, hirsutism, buffalo hump and abdominal striae. Her blood pressure was 170/110 mmHg. Laboratory examination revealed serum potassium level of 2.4 mEq/l. The mean aldosterone to renin ratio was 308 (aldosterone: 98.77 ng/dl, plasma renin activity (PRA): 0.32 ng/ml per h). Intravenous saline infusion test was performed as the confirmatory test. Her post-infusion aldosterone level was 80.69 ng/dl. While the midnight serum cortisol level was 7.6 μg/dl, her serum cortisol levels failed to suppress during a 1 mg dexamethasone suppression test (DST) (5 μg/dl) and 2 mg DST (9.8 μg/dl). Serum ACTH and DHEA-S levels were 13.1 pg/ml and 11.12 μg/dl (*n*: 65–368) respectively. Computed tomography of adrenal glands revealed a 24×14 mm hypodense solid lesion in the right adrenal gland. She underwent laparoscopic right adrenalectomy with perioperative steroid replacement. At the postoperative day 4 at 0800 h, serum cortisol level was 0.6 μg/dl and she was put on substitution therapy with oral glucocorticoids. The aldosterone level and PRA were 2.12 ng/dl and 5.59 ng/ml per h 2 days after the operation, respectively. At the follow-up, her blood pressure and serum potassium level returned to normal.
Conclusion
Patients with A/CPA may present with overt or subclinical hypercortisolism. Therefore, pre-operative screening of cortisol co-secretion in patients with aldosterone-producing adenomas is important to prevent adrenal crises at the perioperative period.

DOI: 10.1530/endoabs.37.EP11

EP12

Comparison of a RIA assay and a CLIA assay for aldosterone determination

Nassima Belaidi, Julie Brossaud, Agnès Georges & Jean-Benoît Corcuff
University Hospital, Bordeaux, France.

Objective
To extend knowledge about the clinical performances of a new chemiluminescent immunoassay (CLIA) for aldosterone set up in available analysers.
Design and patient
We compared the results of a RIA assay to those of a CLIA assay in 198 serum and 80 urine samples from patients in endocrine and hypertension departments. Furthermore, for serum samples the concordance of results for postural tests was analysed.
Results
RIA and CLIA aldosterone serum concentration was linearly correlated with a slope of 0.988 and an intercept of 70.4 pmol/l. The variations of aldosterone serum concentration obtained with the two assays during postural tests were very consistent. There was no significant difference of aldosterone concentrations after thawing with the CLIA. RIA and CLIA aldosterone urine concentrations were linearly correlated with a slope of 0.787 and an intercept of −2.64 nmol/l. Omitting the preservative boric acid from urine samples did not modify aldosterone concentration at least up to 48 h after collection.
Conclusion
The RIA and CLIAs were well correlated for the most useful serum samples. It is well suited to circumvent isotopic assays with the throughput of available analysers.

DOI: 10.1530/endoabs.37.EP12

EP13

Does IGF-1 have a role in ethiopathogenesis of adrenal incidentaloma?

Çiğdem Tura Bahadir & Hulusi Atmaca
Ondokuz Mayis School of Medicine, Samsun, Turkey.

Objectıve
Due to increased usage of imaging modalities today, incidence of adrenal incidentaloma (AI) has increased. Insulin resistance is considered as the etiopathogenic mechanism. Since both insulin and IGF-1 are capable of interacting with same receptors, we aimed to investigate whether IGF-1 has a role in development of adrenal incidentaloma.
Materıals and method
50 female patients with nonfunctional adrenal incidentaloma and 55 acromegaly patients (20 male, 35 female) that admitted to endocrinology outpatient ward between 01/08/2012 and 01/01/2014 and have had undergone abdominal CT or MRI scan were included in this study in addition to a control group of 38 female patients who was performed abdominal CT scan due to urolithiasis. Those patients in adrenal, acromegaly and control groups were analysed regarding age, BMI, waist circumference and serum IGF-1 levels.
Results
Regarding age, no significant difference was present between three groups. BMI and waist circumference (WC) in the control group was lower than those in the acromegaly and adrenal groups ($P<0.001$). Although BMI and WC values were higher in adrenal group, IGF-1 values were significantly higher when compared to the control group ($P<0.001$). Prevelance of adrenal incidentaloma was found to be significantly higher in the acromegaly patients than the control group (25% vs 3%). The results were similar when male patients in acromegaly group are excluded and analysis was conducted only among female subjects. Adrenal incidentaloma prevelance in female acromegaly patients was 34% whereas in the control group it was 3%.
Discussion
In this study, our findings of elevated serum IGF-1 levels in nonfunctional AI patients and higher prevelance of adrenal incidentaloma in acromegaly patients when compared to control group let us think that IGF-1 has a role in the etiopathogenesis of adrenal incidentaloma.

DOI: 10.1530/endoabs.37.EP13

EP14

Effects of megestrol acetate on adrenal function and survival in cancer patients

Guzin Fidan Yaylali[1], Gamze Gokoz Dogu[2], Atike Gokcen Demiray[2], Ahmet Ergin[3], Arzu Yaren[2] & Fulya Akin[1]
[1]Department of Endocrinology and Metabolic Diseases, Faculty of Medicine, Pamukkale University, Denizli, Turkey; [2]Department of Oncology, Faculty of Medicine, Pamukkale University, Denizli, Turkey; [3]Department of Public Health, Faculty of Medicine, Pamukkale University, Denizli, Turkey.

Introduction
Megestrol acetate (MA) has been used in various cancers as a palliative agent to treat cancer cachexia. It has glucocorticoid activity and can induce significant secondary adrenal suppression. We designed this study to determine the extent of adrenal insufficiency in cancer patients receiving MA and find out whether ther was any predictive factor for this.
Methods
Thirty-one patients (11 females and 20 males, aged 48–83 years) who were receiving MA took part in this study. They were evaluated for HPA axis; before the initiation and 1 month later. Serum concentrations of TSH, ACTH, free T_4, cortisol were measured in samples obtained at 0700 h, at baseline and 1st month. Standart ACTH (250 mg) stimulation test was performed if cortisol levels were below 18 μg/dl at any time.
Results
1 month after drug initiation, 32% of patients were accepted as adrenal insufficient. There wasn't any correlation between the basal cortisol, ACTH levels, any biochemical parameter and overall survival. There was negative correlation between 1 month cortisol levels and survival time ($P=0.04$) If cortisol levels were lower at month of theraphy survival time was longer. Cox regression analysis showed that patients having lower cortisol levels at first month had 98% lower risk of death compared to patients having higher cortisol levels ($P=0.02$: OR 0.12 (0.02–0.75)).

Conclusion
It is important to be aware of the effects of MA on adrenal functions and evaluate adrenal functions especially during episodes of infection or after withdrawal of MA therapy since this may require prompt corticosteroid treatment.

DOI: 10.1530/endoabs.37.EP14

EP15

The effect of retinoic acid on human adrenal corticosteroid secretion *in vitro*

Antonella Sesta[1], Laura Tapella[2], Maria Francesca Cassarino[1], Luigi Castelli[3], Francesco Cavagnini[1] & Francesca Pecori Giraldi[1,2]
[1]Neuroendocrinology Research Laboratory, Istituto Auxologico Italiano, Milan, Italy; [2]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; [3]Clinica San Carlo, Paderno Dugnano, Italy.

Retinoic acid, a derivative of vitamin A, has recently yielded promising results in the treatment of Cushing's disease (Pecori Giraldi *et al*. JCEM 2012). Its main site of action appears to be the tumoural corticotrope as retinoic acid inhibits *POMC* transcription and corticotrope proliferation (Paez-Pereda *et al*. JCI 2001). Studies on tumoural adrenal cell lines have revealed an additional inhibitory effect on cell proliferation and stimulated corticosteroid secretion (Paez-Pereda *et al*. JCI 2001). *Aim* of the current study was to evaluate whether retinoic acid modulates corticosteroid secretion by normal human adrenals *in vitro*.
Methods
Primary cultures from nine normal human adrenals were incubated with 10 nM, 100 nM and 1 μM retinoic acid with and without 10 nM ACTH for 24 h. Cortisol levels in medium were measured by Coat-A-Count RIA (Siemens Healthcare Diagnostics, Erlangen, Germany); *CYP11A*, *STAR* and *MC2R* gene expression were analyzed by real-time PCR (7900 HT Sequence Detection System, Applied Biosystems, Foster City, USA) normalized to *RPLP0*.
Results
A clear-cut increase in cortisol secretion during retinoic acid incubation was observed in five adrenal specimens (10 nM: 183.9±55.9%, 100 nM: 210.1±82.6% and 1 μM: 141.3±11.7% baseline). Gene expression analysis revealed a marked decrease in *MC2R* expression (10 nM: 0.65±0.13, 100 nM: 0.63±0.09 and 1 μM: 0.55±0.08 over baseline) and an increase in *STAR* in wells treated with retinoic acid (10 nM: 1.53±0.26, 100 nM: 1.62±0.17 and1 μM: 1.63±0.16 over baseline). *CYP11A* was on average unchanged by retinoic acid. Incubation with ACTH led to a marked increase in cortisol secretion and in *CYP11A1*, *STAR* and *MC2R* expression. Retinoic acid and ACTH co-incubation resulted in a sligthly greater cortisol release (10 nM: 125.4±16.6%, 100 nM: 141.1±29.5% and 1 μM: 139.6±31.3% ACTH) and *MC2R* inhibition (10 nM: 0.76±0.13, 100 nM: 0.56±0.07 and 1 μM: 0.64±0.09 over ACTH) than ACTH alone.
Conclusions
Retinoic acid exerts a stimulatory effect on adrenal corticosteroid secretion *in vitro*, activates *STAR* expression and blunts *MC2R* transcription. This paves the way for novel avenues of research in patients with Cushing's syndrome.

DOI: 10.1530/endoabs.37.EP15

EP16

Adrenal malignant melanoma masquerading as a phaeochromocytoma

Maria Barmpari[1], Christos Savvidis[1], Anastasia Dede[1], Haridimos Markogiannakis[2], Dimitrios Giannopoulos[3], Christina Dikoglou[3] & Sofia Malaktari-Skarantavou[1]
[1]Department of Endocrinology and Metabolism, Hippokration Hospital, Athens, Greece; [2]Department of Endocrine Surgery, First Department of Propaedeutic Surgery, Athens Medical School, Hippokration Hospital, University of Athens, Athens, Greece; [3]Department of Pathology, Hippokration Hospital, Athens, Greece.

Introduction
Adrenal masses usually represent benign and nonfunctional adrenal adenomas however, primary or metastatic malignancy should also be considered. Discovery of an adrenal mass needs further evaluation in order to exclude malignancy and hormonal secretion. Primary adrenal melanoma is an extremely rare entity, while metastases of cutaneous melanoma to the adrenals occur much more often. We present a rare case of a possibly primary adrenal malignant melanoma with imaging and biochemical features of a phaeochromocytoma.
Case report
A 61-year-old male farmer was referred for evaluation of a mass in the right supraclavicular region and a left adrenal lesion. The patient had a history of a multifocal papillary and medullary thyroid carcinoma 3 years before presentation. Genetic analysis for RET mutations was negative. Laboratory tests revealed increased 24-h urinary dopamine and also increased serum calcitonin and neuron specific enolase. The adrenal lesion measured 88.5 mm on MRI, displayed inhomogeneous enhancement of the contrast agent and low diffusion rate. Both lesions appeared positive in In 111-Pentetreotide scintigraphy, while meta-iodo-benzyl-guanidine (MIBG) scintigraphy was negative. Pathologic examination of the resected right supraclavicular mass and left adrenal was consistent with malignant melanoma. Rough evaluation for a primary melanoma site was negative.
Conclusion
This is the case of a possibly primary adrenal malignant melanoma with imaging and biochemical features of a pheochromocytoma. Melanocytes and chromaffin cells share a common embryological origin and in melanoma tissue there is expression of tyrosine hydroxylase leading to production of DOPA and melanins. Although this case is very rare, and there are rigid diagnostic criteria for the diagnosis of primary adrenal melanoma, the differential diagnosis of a dopamine secreting adrenal mass should include primary or metastatic malignant melanoma in order to determine the best diagnostic approach to the patient and select the most appropriate surgical management.

DOI: 10.1530/endoabs.37.EP16

EP17

Cushing's disease: experience in a third level hospital from Zaragoza (Spain)

Francisco Losfablos Callau[1], Paloma de Castro Hernández[2], Pablo Trincado Aznar[2], Marta Monreal Villanueva[2] & Javier Acha Pérez[2]
[1]Calatayud Hospital, Zaragoza (Aragón), Spain; [2]Miguel Servet Hospital, Zaragoza (Aragón), Spain.

Objective
Cushing's disease (CD) is caused by pituitary corticotrophin (ACTH)-secreting tumours. Our aim is to show our experience in a third level hospital attending a 500 000 based population area from 1990 to now.
Methods
We review retrospectively the medical reports of all patients diagnosed as CD from 1990 by a data collection protocol. We reject the reports without enough or inadequate information. We present results by using descriptive statistics.
Results
29 patients were diagnosed as CD in the period study (estimate average incidence of 2.41 cases/million people per year). Nine medical reports contain insufficient or misleading information including two from dead patients. The remaining 20 patients were included in our analysis. Mean age at diagnosis was 39 years (range 17–75 years) with a bimodal distribution. Mean BMI was 28.45 kg/m^2. Mean follow up time was 11 years (range 2–24). 90% were women. Reference most common reason was hyperandrogenism (acne and hirsutism, 55%). Most common symptom were also hirsutism, 65%. Mean plasma basal cortisol value was 27.9 μg/dl (range 18–51 μg/dl). Mean basal cortisol value after 1 mg of DXM was 14.6 μg/dl (3.38–34.9 μg/dl). Mean basal cortisol value after 4 mg of DXM was 14.53 μg/dl (3.08–23.46 μg/dl). Mean basal cortisol value after 8 mg of DXM was 7.96 μg/dl (0.34–24.45 μg/dl). Mean 24-h urinary free cortisol value was 840.7 μg/24-h (97–5530 μg/24-h). Mean cortisol value at midnight was 13.63 μg/dl (9.26–18.03 μg/dl). Mean ACTH value was 71.96 pg/dl (20–231 pg/dl). 35% of tumours were not visible at MRI, 55% were microadenomas and 10% macroadenomas. 95% of patients were treated surgically. The ratio of curation after the first surgery was 65%. One patient (5%) was treated only pharmacologically (ketoconazole) and remain controlled after 9 years of follow up. 30% of patients required a second treatment. Mean time to this second treatment was 5.32 years (range 0.3–12 years). 30% of patients required a second surgery with a curation rate of 50%. 15% of patients have required radiotherapy and 5% bilateral adrenalectomy. 15% of patients remain with hypopituitarism and 35% with hydrocortisone supplementation.
Conclusions
Our patients reproduce well referenced data from other series. Hiperandrogenism was the main cause of consultation.

DOI: 10.1530/endoabs.37.EP17

EP18

Subclinical Cushing's syndrome and clinical implications in bilateral compared to unilateral adrenal incidentalomas: a meta-analysis

Stavroula A Paschou[1], Eleni Kandaraki[1], Fotini Dimitropoulou[1], Dimitrios G Goulis[2] & Andromachi Vryonidou[1]
[1]Department of Endocrinology and Diabetes, Hellenic Red Cross Hospital, Athens, Greece; [2]Unit of Reproductive Endocrinology, First Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece.

Introduction
The aim of this study was to systematically review the literature for studies that have investigated possible differences in prevalence of subclinical Cushing's syndrome (SCS) and related clinical implications between patients with unilateral (UAI) and bilateral adrenal incidentalomas (BAI) and to meta-analyze the best evidence available.
Methods
Electronic databases PubMed, MEDLINE and EMBASE were systematically searched. Main study outcome was the prevalence of SCS in patients with UAI and BAI. Secondary outcomes were the prevalence of obesity, diabetes, glucose intolerance, hypertension, dyslipidaemia and osteoporosis in patients with UAI and BAI. Random effects odds ratios (OR) or standardized mean differences (SMD) and 95% CI were calculated. Meta-analysis was conducted using Review Manager (RevMan 5.3).
Results
Six studies were included in the meta-analysis involving in total 1239 patients, 968 with UAI and 271 with BAI. Patients with UAI had lower prevalence of SCS compared with those with BAI (OR (95% CI) 0.51 (0.32; 0.81), $I^2=55\%$). The mass diameter of UAI did not differ from BAI (the size of the largest lesion) (SMD (95% CI) −0.40 (−0.97; 0.17), $I^2=91\%$). The prevalence of obesity (SMD (95% CI) 0.06 (−0.10; 0.22), $I^2=0\%$), diabetes (OR (95% CI) 0.78 (0.51; 1.21), $I^2=0\%$), hypertension (OR (95% CI) 1 (0.47; 2.12), $I^2=74\%$) and dyslipidaemia (OR (95% CI) 0.93 (0.49; 1.78), $I^2=49\%$) did not differ between UAI and BAI.
Conclusions
Patients with BAI present a higher prevalence of SCS compared to patients with UAI, without any differences in related clinical implications.

DOI: 10.1530/endoabs.37.EP18

EP19

Association of psoriasis with Cushing's syndrome

Cigdem Tura Bahadir, Feyzi Gokosmanoglu, Elif Kilic Kan, Gulcin Cengiz Ecemis, Aysegul Atmaca, Hulusi Atmaca & Ramis Colak
Ondokuz Mayis University, Samsun, Turkey.

Introduction
Psoriasis is a chronic, inflammatory and T-cell mediated autoimmune disease of skin. Its prevalence is 2–3%. It may improve due to immunesupressive effects of hypercortisolaemia during the active phase of Cushing's syndrome (CS) and may exacerbate after treatment. The aim of this study was to investigate association of psoriasis with CS.
Methods
We prospectively followed 62 patients who had been diagnosed with CS between 2010 and 2014 in our clinic. Of the patients, 60% was Cushing disease (CD) (29 female, eight male) and 40% was ACTH-independent CS (20 female, five male). The patients were evaluated for psoriasis.
Results
The prevalence of psoriasis was 5% among our patients with CS. Psoriasis was diagnosed in three patients; two had pituitary adenoma and one had adrenal adenoma. Two were diagnosed before treatment of CD, and the other was diagnosed after 2 years following remission of ACTH-independent CS. The pathological evaluation of two patients with CD was reported as densely granulated corticotrophic adenoma and the pathological evaluation of the patient with ACTH-independent CS was reported as adrenocortical adenoma with nuclear pleomorphism and possible malignant behaviour. In the light of these findings, potential hypersecretory tumours should be considered.
Discussion
Endogenous hypercortisolism supresses inflammatory response and induces a state of immunesuppression. Once cortisol levels come back to normal following remission of CS, rebound response of immunity may result in exacerbation of autoimmune diseases like psoriasis. Prevalence of psoriasis is elevated in CS. If the patient is known to have a history of stress-responders psoriasis prior to surgery, we should evaluate the patient more carefully and frequently for exacerbation of psoriasis after remission of CS. Autoimmune diseases may exacerbate or may be newly diagnosed because of rebound immunity in remission of CS.

DOI: 10.1530/endoabs.37.EP19

EP20

Should Cushing syndrome be only evaluated by endocrinologists and neurosurgeons?

Cigdem Tura Bahadir, Feyzi Gokosmanoglu, Elif Kilic Kan, Gulcin Cengiz Ecemis, Aysegul Atmaca, Hulusi Atmaca & Ramis Colak
Ondokuz Mayis University, Samsun, Turkey.

Objective
Physical features such as central obesity, purple stria, thin skin, moon face and buffalo hump may be observed in Cushing's syndrome (CS). Psychiatric and psychological disturbances may also be present in addition to the physical problems. The most common mental disturbance is major depression. Mania and anxiety disorders may also be seen. It may be detected both in active period or in remission of CS on account of persistent effect of previous period of hypercortisolism, hypopituitarism and glucocorticoid deficiency. In this study, we aimed to analyse the frequency of psychopathologic disorders in CS.
Methods
We prospectively followed 62 patients that had been diagnosed with CS between 2010 and 2014 in our clinic. Of the patients, 60% were Cushing's disease (CD) (29 female, eight male) and 40% were ACTH-independent CS (20 female, five male). The patients who had been under medication for psychopathology were included in the study.
Results
The prevalence of psychopathology was 19% in CS (12 patients). In ACTH-independent CS and CD it was 12 and 24%, respectively. Eleven (92%) patients were female. Nine (75%) patients had active diseases. Two patients, one with CD and one with ACTH-independent CS, had history of suicide attempts 1.5 and 2 years after surgery, respectively. Both suicide attempts happened after surgery. The patients who attempted suicide had glucocorticoid deficiency and hypopituitarism, respectively.
Discussion
In CS patients, psychiatric and psychological disorders may be seen before or after treatment. Despite treatment for CS, they still may have severe psychopathologic disorders to the degree of suicide attempts due to hormonal insufficiencies in the postoperative period that may result from medication or surgical complications. For this reason, patients should be evaluated not only by endocrinology and neurosurgery clinics, but also psychiatry clinics both before and after the surgery.

DOI: 10.1530/endoabs.37.EP20

EP21

Necessity of thrombophylaxis in Cushing's syndrome

Cigdem Tura Bahadir, Feyzi Gokosmanoglu, Elif Kilic Kan, Gulcin Cengiz Ecemis, Aysegul Atmaca, Hulusi Atmaca & Ramis Colak
Ondokuz Mayis University, Samsun, Turkey.

Introduction
Cushing's syndrome (CS) is accompanied by a ten times increased risk of venous thromboembolism and arterial thrombosis. In this study we aimed to analyze frequency of thromboembolism in CS.
Methods
We prospectively followed 62 patients who had been diagnosed with CS between 2010 and 2014 in our clinic. Of the patients, 60% had Cushing's disease (CD) (29 females and eight males) and 40% had ACTH-independent CS (20 females and five males). Frequencies of arterial and venous thromboembolic events were recorded.
Results
The prevalence of thromboembolic events was 5% in our patient population. Thromboembolism was diagnosed in three patients (two CD and one ectopic CS); one with venous thromboembolism, two with arterial thrombosis (Table 1). Two of them were diagnosed in the postoperative period, but one of them was suspected to have the event before the surgery. Remaining one of the three patients was diagnosed with recurrent pulmonary thromboembolism both before and after surgery for CS.

Table 1 Location and time of thromboembolism in our patient population.

					Time of diagnosis	
	Age/ sex	Aetiology of CS	Vessel	Thromboembolic event	Preoperative period	Postoperative period
1	45-F	Pituitary adenoma	Venous	DVT of lower extremity	-	After 4 months
2	40-M	Pituitary adenoma	Arterial	Subacute thrombosis of external iliac artery	-	After 1 week
3	42-M	Ectopic	Arterial	Fatal PTE	Before 9 months	After 2 weeks

DVT, deep venous thrombosis; PTE, pulmonary thromboembolism.

Discussion
Thromboembolism may occur before and after surgery in CS. It generally occurs in the first year, especially in the first 3 months following surgery. It may be venous or arterial in origin. Thus, thromboprophylaxis should be administered to patients with active CS before and after the surgery for 6 months.

DOI: 10.1530/endoabs.37.EP21

EP22

Short Synacthen testing: are we referring appropriately and over diagnosing adrenal insufficiency?

Abu Saeed, Sara Guthrie, Oliver Pickles & Parijat De
City Hospital, Birmingham, UK.

Background
A previous short Synacthen test (SST) audit in our hospital (2012) showed 70% of initial SST tests were normal with 9% inappropriate requests. A new pro forma was devised whereby one of four criteria (specific symptoms, medications, previous diagnosis, and physical findings) had to be satisfied to be able to undergo a SST. Additionally, we noticed that a number of patients were probably being over-diagnosed wth adrenal insufficiency (AI) based on a single 30 min cortisol estimation following SST.
Aims
To evaluate if this new pro forma helped reduce inappropriate referrals for SST and whether the added value of 60 min cortisol (rather than only 30 min) helped minimise overdiagnosis of AI.
Method
The results of this new proforma and a full SST incorporating both 30 and 60 min cortisol following SST were collected and analysed between Sept and Nov 2014.
Results
All 27 requests (100%) for SST were appropriate. 63% (17/27) of patients had an abnormal result at 30 min and 44% (12/27) at 60 min. 12 patients (44%) had both abnormal 30 and 60 min cortisol results (five on steroids, five asymptomatic, four with pituitary pathology, three hyponatremia, and one each with hypotension, T1DM and and new pigmentation). 18% (5/27) had an abnormal result at 30 min but a normal result at 60 min. 4/6 patients referred with hypotension/hyponatremia had abnormal SST result. 7/7 patients who satisfied only the 'symptoms' criteria had a normal SST result whereas 0/5 patients who satisfied the 'symptoms' criteria and at least one other criteria had a normal result.
Conclusion
The new pro forma has made the referral system more effective. Nearly a fifth of over diagnosis of AI can be prevented by routinely measuring serum cortisol at 60 min. By selecting symptomatic patients who satisfied at least one other criteria will also further help minimise unnecessary SSTs.

DOI: 10.1530/endoabs.37.EP22

EP23

Primary hyperaldosteronism: predictors of response to therapy in Singapore

Minyang Chow[1,2], Grace Lum[2] & Rinkoo Dalan[1]
[1]Tan Tock Seng Hospital, Singapore, Singapore; [2]National University of Singapore, Singapore, Singapore.

Background
Primary hyperaldosteronism is a common cause of secondary hypertension, accounting for up to 5% of cases locally. It is treated medically with spironolactone and/or amiloride, or surgically with adrenalectomy. This study determines the prognostic factors for response to treatment, resulting in reduction of blood pressure to normotensive levels.
Methods
We retrospectively reviewed records of 57 patients who were diagnosed with primary hyperaldosteronism by a saline suppression test, and subsequently underwent treatment. The patients were divided into two groups – hypertensive and normotensive (WHO $<140/90$), based on their blood pressure readings at 1 year since starting treatment. We collected baseline characteristics of both groups, including patient demographics – age, gender, race, BMI, as well as medical comorbidities, use of anti-hypertensive medications, and results of screening and diagnostic tests, and compared them via multivariate analysis.
Results
At 1 year post treatment, 28 (49.1%) patients were normotensive, and 29 (50.9%) were hypertensive. We found that the hypertensive group had more person-years of diabetes (mean $=2.52$ vs 0.41, $P<0.05$), and also had a higher baseline aldosterone level (mean $=749.15$ vs 532.61, $P<0.05$), than the normotensive group. Other factors, including the patient age, gender, race, BMI, baseline blood pressure, years of hypertension, number and type of antihypertensive medications, baseline creatinine, potassium, sodium, renin, saline suppression test results, treatment type, presence of adenoma on CT scan, did not differ significantly between the two groups.
Discussion and conclusion
In patients diagnosed with primary hyperaldosteronism, predictors for achieving normotension with treatment include not having or having fewer years of diabetes, and having a lower baseline aldosterone level. This knowledge is helpful for physicians to prognosticate response to treatment in newly diagnosed patients.

DOI: 10.1530/endoabs.37.EP23

EP24

Reduced salivary cortisone, but similar cortisol day curves in Addison's disease in patients on hydrocortisone replacement

Ian Ross[1], Miguel Lacerda[1], Tahir Pillay[1,2], Dirk Blom[1], Gudmundur Johannsson[3], Joel Dave[1], Naomi Levitt[1], David Haarburger[4] & Jan-Stefan van der Walt[5]
[1]University of Cape Town, Cape Town, South Africa; [2]NHLS, Tshwane, South Africa; [3]University of Gothenburg, Gothenburg, Sweden; [4]Ampath Laboratories, Pomona, South Africa; [5]Astellas Pharma, Leiden, The Netherlands.

Background
Salivary cortisol, as measured using electro-chemiluminescence has been used to monitor patients with Addison's disease (AD) on hydrocortisone replacement. Salivary cortisone has been suggested as an alternative to salivary cortisol, as it may accurately reflect plasma free cortisol. We wished to examine the pharmacokinetics of these analytes in patients and controls.
Methods
We measured salivary cortisol and salivary cortisone by liquid chromatography–tandem mass spectrometry using a day curve with 16 time points in patients with AD on hydrocortisone and in healthy controls with endogenous cortisol secretion.
Results
There were 25 patients and 26 healthy controls. The median (interquartile range) area under the curve (AUC) for cortisol was not different for patients, 55.63 (32.91–151.07), compared with controls 37.49 (27.41–52.00) nmol/min per l; $P=0.098$, whereas the peak cortisol (Cmax) was higher 32.61 (5.75–146.19) nmol/l vs 8.96 (6.96–12.23) nmol/l; $P=0.013$ and time to peak (Tmax) 1.5 (0.5–2.0), compared with controls 0.0 (0.0–0.5) h; $P<0.001$. The AUC for cortisone was reduced for patients, 23.65 (6.10–54.76), compared with controls, 227.73 (200.10–280.52) nmol/min per l; $P\leq0.001$, Cmax for cortisone was lower 11.11 (2.91–35.85) nmol/l vs 33.12 (25.97–39.95) nmol/l; $P=0.002$ and longer Tmax 2.5 (2.0–9.5), compared with 0.25 (0.00–0.50) h, respectively; $P<0.001$.
Conclusions
Although there was no difference in cortisol exposure, there was less cortisone exposure in patients than controls, possibly due to the pharmacological effect of hydrocortisone on the 11-β-hydroxysteroid dehydrogenase enzymes. Lack of cortisone exposure and less metabolism of cortisol in patients with AD may predispose to metabolic consequences.

DOI: 10.1530/endoabs.37.EP24

EP25

Problems in ACTH–ectopic syndrome diagnostics in clinical practice

Natalya Volkova, Ilya Davidenko & Maria Porksheyan
Rostov State Medical University, Rostov-on-Don, Russia.

Introduction
Cushing's syndrome describes symptoms associated with prolonged exposure to inappropriately high levels of cortisol. It may be increased as a result of high ACTH production in the pituitary gland or from tumours outside pituitary–adrenal system.
Case report
Patient 34 years old was hospitalised with complaints of muscle weakness, shooting-pain in thoracic, lumbar spine, decreased height, amenorrhea, arterial hypertension and change in appearance at September 2009. The first symptom of disease was elevated blood pressure at 2007. Patient marked appearance of red striae at July 2009. Next month, compression fracture of five to nine thoracic vertebras was founded based on MRI. At the same time, increased level of ACTH was revealed, but his fact was disregarded. Thus, it was passed 2 years from first complaints to supposition of Cushing's syndrome. In the hospital, as a result based on positive suppression test with dexamethasone 1 mg and positive test with desmopressin, ACTH–ectopic syndrome was diagnosed. In the same time, tumour of central mediastinum was revealed. Patient was operated, but histology found out, that this tumour consisted of adipose tissue. Patient was repeatedly hospitalized with same complaints at October 2010. New attempts of revealing ACTH-productive tumour was become unsuccessful again. Thus, left-side laparoscopic adrenalectomy was performed 6th October 2010. Right-side laparoscopic adrenalectomy was done in 2 weeks. Hormonal replacement therapy (prednisolone 30 mg/daily) was prescribed after surgery. But, acute adrenal insufficiency was developed in 3 weeks, and patient died. Clinical diagnosis was confirmed on autopsy. But, ACTH-productive tumour wasn't revealed.
Conclusion
This clinical case demonstrates problems in ACTH–ectopic syndrome diagnostics. it was passed 2 years since first complaints until supposition of Cushing's syndrome, despite of typical clinical signs in this patient. Also, there is no common guideline of ACTH–ectopic syndrome. Lingering search of tumour delayed decision making about two-sided laparoscopic adrenalectomy.

DOI: 10.1530/endoabs.37.EP25

EP26

Primary adrenal lymphoma: case report

Rosa Márquez-Pardo, Maria-Gloria Baena-Nieto, Manuel Cayón-Blanco, Lourdes García-García-Doncel, Rosario López-Velasco & Isabel Torres-Barea
Jerez Hospital, Jerez, Cadiz, Spain.

Introduction
Malignancy is an uncommon cause of adrenal incidentaloma in patients without a known diagnosis of cancer. The actual frequency of primary adrenal carcinoma in patients with adrenal incidentaloma is ∼2–5%; another 0.7–2.5% have nonadrenal metastases to the adrenal gland. The presence of a nonadrenal primary tumour is exceptional and has been scarcely reported in medical literature.
Case report
We present a case of 71-year-old male who presented with fatigue, anorexia, weigh loss, and hypotension. Initial laboratory evaluation didn't reveal any anormal result. Computed tomography (CT) scans of the abdomen and pelvis demonstrated large bilateral adrenal masses (the right adrenal gland measured $15\times8.6\times7$ cm and the left adrenal gland measured $11.6\times6.5\times6$ cm). The masses were nonfunctional according to hormone test results (cortisol of 270 mmol/l, ACTH level of 92.18 pmol/l, 24 h urinary level of normetanephrine 425 μg/day, and metanephrine 148 μg/day). The laboratory test showed adrenal insufficiency (plasma cortisol of 267.62 nmol/l; cortisol failed to increase during the ACTH stimulation test (267.62–226.23 nmol/l) and ACTH was elevated (79.03 pmol/l). A CT-guided core needle biopsy of the left adrenal mass was performed and revealed diffuse large B-cell lymphoma. Bone marrow biopsy was negative for lymphomatous involvement. An F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) scan showed intense FDG accumulation in both adrenal glands (SUV 24.6), there was no abnormal FDG uptake in the rest of the body.
Conclusions
Primary adrenal lymphoma is a very rare extranodal lymphoma, generally occurring among patients of advanced age (mean: 68 years) and dominantly in males. The most frequently histological type is diffuse large B-cell B lymphoma and is usually bilateral. Prognosis is poor. Treatment consist in chemotherapy regimens (the most common regimen is CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)) and in some cases treatment with surgery and radiotherapy is necessary.

DOI: 10.1530/endoabs.37.EP26

EP27

Cushing's syndrome and diabetes

Said Azzoug, Leyla Rabehi, Sara Hannachi, Houda Medjdoubi & Farida Chentli
Endocrinology and Metabolic Diseases Department, Bab El Oued Hospital, Algiers, Algeria.

Introduction
Cortisol has numerous actions on glucose metabolism and insulin action which explain the frequency of glucose abnormalities in Cushing's syndrome (CS). The aim of our work was to assess the prevalence and characteristics of diabetes in CS.
Material and methods
This is a retrospective study concerning 51 CS (44F/7M) in whom we looked for the presence of diabetes either by fasting glycaemia or 75 g oral glucose tolerance test. Thereafter, we looked for the characteristics of diabetes in CS. CS was secondary to Cushing's disease in 82% and to adrenal adenoma in 18%.
Results
55% of patients have diabetes. Among diabetic patients, 39% have high blood pressure and 42% have a family background of diabetes. 40% of diabetics were treated with oral treatment, 25% with insulin and 35% were on life style therapy. Mean age was 31.92 ± 10.26 years; it was 31.62 ± 10.54 years in patients with diabetes vs 32.45 ± 10.04 years in patients without diabetes. Mean BMI was 31.47 ± 7.33 kg/m^2; it was 31.30 ± 7.77 kg/m^2 in patients with diabetes vs 31.89 ± 6.47 kg/m^2 in patients without diabetes. Diabetic retinopathy was present in 10% and diabetic neuropathy in 5%. After treatment of CS diabetes resolved in 40% and persisted in 60%.

Conclusion
Diabetes mellitus is frequent in cortisol excess states, the high frequency of diabetes in our study may be explained by preexistent undiagnosed diabetes as diabetes persisted in 60% after resolution of CS.

DOI: 10.1530/endoabs.37.EP27

EP28

Cushing's syndrome and dyslipidaemia

Said Azzoug, Leyla Rabehi, Sara Hannachi, Houda Medjdoubi & Farida Chentli
Endocrinology and Metabolic Diseases Department, Bab El Oued Hospital, Algiers, Algeria.

Introduction
Cortisol activates lipolysis in adipose tissue resulting in the release of free fatty acids into the circulation, it also activates cholesterol and triglycerides synthesis. The consequence is an increase in total circulating cholesterol and triglycerides with their inherent risks on the cardiovascular system. The aim of our work was to assess the prevalence and characteristics of dyslipidaemia in Cushing's syndrome (CS).
Material and methods
This is a retrospective study concerning 51 CS (44F/7M) in whom we looked for the presence of hypertriglyceridemia (triglycerides level ≥ 1.50 g/l) and/or hypercholesterolemia (total cholesterol level ≥ 2 g/l). Thereafter we looked for the characteristics of dyslipidaemia in CS. Their mean age was 32.34 ± 10.42 years. CS was secondary to Cushing's disease in 82% and to adrenal adenoma in 18%.
Results
53.12% of patients have hypertriglyceridemia. Triglycerides level was between 1.50 and 1.99 g/l in 41.17% and ≥ 2 g/l in 48.83%. 88.23% of hypertriglyceridemic patients have diabetes and hypertension. 51.61% of patients have hypercholesterolemia. 68.75% of hypercholesterolemic patients have hypertriglyceridemia, 87.5% have diabetes, and 87.5% have hypertension.
Conclusion
Dyslipidaemia is frequent in CS. Hypertriglyceridemia and hypercholesterolemia are frequently associated with hypertension and/or diabetes, which may explain the increased risk of cardiovascular disease in cortisol excess states.

DOI: 10.1530/endoabs.37.EP28

EP29

Cushing's syndrome and hypertension

Said Azzoug, Leyla Rabehi, Sara Hannachi, Houda Medjdoubi & Farida Chentli
Endocrinology and Metabolic Diseases Department, Bab El Oued Hospital, Algiers, Algeria.

Introduction
Patients with Cushing's syndrome (CS) are prone to hypertension as cortisol stimulates renal reabsorption of sodium and enhances vascular sensitivity to catecholamine and angiotensin II. This explains the frequency of hypertension in patients with CS. The aim of our work was to assess the prevalence and characteristics of hypertension in CS.
Material and methods
This is a retrospective study concerning 51 CS (44F/7M) in whom we looked for the presence of high blood pressure (HBP). Thereafter, we looked for the characteristics of HBP in CS. CS was secondary to Cushing's disease in 82% and to adrenal adenoma in 18%.
Results
HBP was present in 67%. Among hypertensive patients, 33% have diabetes mellitus and 33% have a background of familial hypertension. Mean age was 32.03 ± 9.87 years and mean BMI was 30.77 ± 6.58 kg/m^2. HBP was treated with one anti-hypertensive drug in 41% and two or more anti-hypertensive drugs in 33%. In 26% patients were treated with life style therapy only. 12% have hypertensive retinopathy, 5% have nephropathy, and 9% have cardiovascular disease. After treatment of CS hypertension persisted in 45% and resolved in 55%.
Conclusion
Hypertension is frequent in CS, it's association with diabetes, dyslipidaemia and a pro-coagulant state also frequent in CS explain the high frequency of cardiovascular events in hypercortisolism states.

DOI: 10.1530/endoabs.37.EP29

EP30

Asymmetric dimethylarginine level and markers of atherosclerosis in Cushing's syndrome

Cemile Ozsurekci[1], Mujde Akturk[1], Cigdem Ozkan[1], Ozlem Gulbahar[2], Alev Altinova[1], Muhittin Yalcin[1], Emre Arslan[1] & Fusun Toruner[1]
[1]Department of Endocrinology, Faculty of Medicine, Gazi University, Ankara, Turkey; [2]Department of Biochemistry, Faculty of Medicine, Gazi University, Ankara, Turkey.

Objective
Cushing's syndrome (CS) is related to diabetes mellitus, dyslipidaemia, hypertension, and obesity, which lead to cardiovascular disease (CVD). CVD is the major cause of mortality and morbidity in CS. The aim of our study was to investigate CVD risk markers, such as asymmetric dimethylarginine (ADMA), lipoprotein-associated phospholipase A2 (Lp-PLA2), highly sensitive C-reactive protein (hsCRP), homocysteine, lipid levels, ankle-brachial index (ABI), and carotid intima–media thickness (CIMT) in CS.
Methods
Our study included 27 patients with active CS and age, sex, BMI, and co-morbid diseases matched 27 control patients.
Results
Plasma ADMA levels were significantly lower in CS compared to the control group ($P = 0.013$). Total cholesterol, LDL cholesterol, HDL cholesterol, apo A1, and apo B levels were higher in patients with CS than the control group ($P < 0.05$). We did not find any statistically significant difference in hsCRP, Lp-PLA2, and homocysteine levels, CIMT and ABI measurements between CS and control groups ($P > 0.05$).
Conclusion
Our results suggest that CVD in CS may occur primarily due to comorbid diseases with CS. We found that ADMA levels were lower in CS than co-morbid diseases matched control group, which should be further investigated.
Disclosure
This project was supported by IMSED (Internal Medicine Postgraduate Education Association).

DOI: 10.1530/endoabs.37.EP30

EP31

A case of aldosterone-secreting giant adrenal carcinoma: a case report

Mehtap Evran, Gamze Akkus, Murat Sert & Tamer Tetiker
Cukurova University, Adana, Turkey.

Introduction
Primary aldosteronism is presented with signs of hypertension and hypokalaemia classically, however, primary adrenal carcinoma is very rare condition. We aimed to present a patient with a metastatic adrenal carcinoma after the primary diagnosis of hyperaldosteronism.
Case report
A 46 years old male patient was referred to our hospital with weakness, dry mouth and weight loss. He had lost weight as 31 pounds during last 3 months. Physical examination revealed diffuse crackles in lungs. The others system examination was found normal without any organomegaly or lymphadenopathy. Arterial tension was measured 170/100 mmHg, serum sodium 140 mEq/dl, potassium 1.9 mEq/dl at admission. Differential diagnosis was planned on uncontrolled hypertension and persistent hypokalaemia with elevated aldosterone levels and low renin levels as 753 ng/dl (3–28 ng/dl) and 0.57 ng/ml per h (0.65–5 ng/ml per h) respectively. After potassium replacement therapy, potassium was 3.1 mEq/dl. Doxazosin 8 mg/day with spironolactone 100 mg/day was started. Supression was established with 1 mg dexamethasone in cortisol level. In thorax–abdominal CT was showed bilateral diffuse nodules (biggest was nearly $\sim$2.5 cm) in lungs were consisted with metastatic cancer. A giant mass with 12 cm diameter in suprarenal region, which involves liver partially, consisted with adrenal gland tumour was determined. The miliary tuberculosis ruled out by bronchoscopy. Metastatic multiple hyper-metabolic lesions in lungs and hyper-metabolic mass in surrenal region were detected in positron emission tomography. Fine needle aspiration biopsy was performed from right surrenal

mass with CT scan. Pathology revealed adrenocortical carcinoma. Chemotherapy (mitotane) was the chosen treatment because of the distant metastases. Patient died during the chemotherapy.
Conclusions
Primary adrenal carcinoma is very rare with annual incidence of one per one million populations. Less than 1% of all secrete aldosterone. Also clinicians should be aware that primary hyperaldosteronism could occur in the context of adrenocortical carcinoma.

DOI: 10.1530/endoabs.37.EP31

EP32

The incidence and characteristics of adrenal insufficiency among patients with suspicious symptoms in general hospital in Korea

Namkeong Kim, MiKyung Kim, Nanhee Cho, YeYeon Lee & Hyesoon Kim
Keimyung Medical School, Daegu, Republic of Korea.

Objective
Adrenal insufficiency is the clinical manifestation of deficient production or action of glucocorticoids, with or without mineralocorticoids deficiency and adrenal androgens. The mortality of untreated adrenal insufficiency reaches up to 80% in 2 years. Moreover, the symptom is non-specific like malaise, dizziness. Therefore, history taking, prompt diagnosis and management are more important. The diagnostic investigation, although well established, can be challenging, especially in patients with secondary or tertiary adrenal insufficiency. However, information about the prevalence and characteristics of adrenal insufficiency in Korea is lack. Therefore, we reviewed the characteristic of patients of adrenal insufficiency.
Methods
We reviewed medical records of patients who visited Keimying University Dongsan Medical Center for 4 months and conducted a test such as rapid ACTH stimulation test and insulin tolerance test.
Results
In 267 participants enrolled, most common reason (38.9%) to conduct a test was that patients complained suspicious symptoms related with adrenal insufficiency and the second reason (29.6%) was for diagnosis the cause of hyponatremia. Among them, 37.4% patients was diagnosed as adrenal insufficiency. 70% was female and mean age was 65.23 years old. Basal cortisol level was 3.93 ± 3.81 and it was significantly lower than normal patients ($P = 0.000$). Common symptoms are anorexia, nausea, dehydration, and arthralgia. 67% patients had history of steroid medication and 53% of patients took steroid within 3 months.
Conclusion
A lot of patients who diagnosed adrenal insufficiency are related with steroid medication. History taking about long-term use of steroid is necessary for early detection. Basal cortisol level could not be diagnosis but provide an useful clue for diagnosis of adrenal insufficiency. In addition, when we use steroid, we are more cautious about development adrenal insufficiency. We need further study to evaluate the prevalence and characteristics in a large population.

DOI: 10.1530/endoabs.37.EP32

EP33

A case of Addison's disease: high clinical suspicion should guide diagnosis and caution should be used when reviewing initial laboratory investigations

Mark Sutton-Smith, Maria Ravelo, David Lipscomb & Naik Haya
East Sussex Healthcare NHS Trust, The Bending and Sheppard Centre for Diabetes and Endocrinology, Kings Drive, Eastbourne, East Sussex BN21 2UD, UK.

A 69-year-old lady with a history of autoimmune diabetes mellitus and primary autoimmune hypothyroidism presented to the Specialist Diabetes Clinic with a significant inexplicable variation in her capillary blood glucose. She had been undergoing investigations with the gastroenterologists for nausea, vomiting, and weight loss. Despite extensive investigations including: oesophageal–gastro-duodenoscopy, CT–thorax, abdomen, pelvis scanning, and gastric emptying studies no cause for her symptoms had been found. Her drug therapy included ranitidine, omeprazole, metformin, levothyroxine, folic acid, simvastatin, lantus, and novorapid. Given her clinical presentation and autoimmune diagnoses, metformin was stopped and she was investigated for adrenal insufficiency. Her basal serum cortisol was 410 nmol/l (normal range >400 nmol/l). Her short Synacthen test results were 421 nmol/l at 30 min and 433 nmol/l at 60 min. Basal ACTH 1100 ng/l (normal range 5–46), plasma renin 28 nmol/l per h (normal range 0.5–3.1), and plasma aldosterone 110 pmol/l (normal range 100–800). Anti-adrenal antibody titre was positive at 1:10 dilution.
Discussion
Baseline serum cortisol level was perceived to be adequate; however response to ACTH was stunted. The ACTH, aldosterone, and renin levels together with positive anti-adrenal antibody titre are consistent with a diagnosis of primary autoimmune adrenal insufficiency (Addison's disease). She was immediately started on hydrocortisone replacement with explanation about steroid sick day rules, mineralocorticoid was added and she was reviewed in clinic 3 weeks later. Her glycaemic profile improved, hypoglycaemic episodes were abolished and gastroenterological symptoms completely resolved. This case highlights the importance of retaining a high degree of clinical of suspicion in diagnosing adrenal insufficiency despite a 'normal' basal cortisol and how ACTH, aldosterone, renin, and anti-adrenal antibody testing may aid diagnosis in such cases.

DOI: 10.1530/endoabs.37.EP33

EP34

Selective adrenal venous sampling is not always useful in primary aldosteronism

Miguel Paja[1], Borja Peña[2], Laura A Calles[1] & Cristina Moreno[1]
[1]Endocrinology Department, Hospital Universitario de Basurto, Bilbao, Basque Country, Spain; [2]Radiology Department, Hospital Universitario de Basurto, Bilbao, Basque Country, Spain.

Adrenal venous sampling (AVS) is regarded as the gold-standard for the study of lateralisation of primary aldosteronism (PA) after its biochemical diagnosis. After catheterisation of both adrenal veins, confirmed by ratio of cortisol concentration in each adrenal vein and peripheral vein (selectivity index (SI)), lateralization is accepted if aldosterone/cortisol (A/C) ratio between both adrenal veins is over 3–4 (lateralization index (LI)), particularly if non-dominant vein has A/C level lower than peripheral vein. We present two cases of PA with selective AVS, but puzzling results about lateralisation: case 1 – woman (52 years), severe hypertension for the last 2 years, with elevated ratio aldosterone/plasmatic renin activity (RAR) and urinary aldosterone of 16.4 μg/24 h with hypernatriuria (340 mEq/24 h). First sample showed right SI of 44.3 and left SI of 12.2, and suggested bilateral production (LI: 1.12), with both adrenal A/C levels higher than peripheral vein. Second sample, 5 min later, showed right SI of 18.9 and left SI of 10.3, but indicated right lateralisation (LI: 3.2), coincident with adrenal tumour in CT, with A/C ratio in left vein lower than peripheral A/C ratio. Case 2 – woman (52 years), severe hypertension, only one selective sample in AVS (right SI: 10.83 and left SI: 15.32), A/C ratio in both veins lower than peripheral vein (18.2 and 8.5 vs 71.9). Normal CT scan. These two cases illustrate potential inaccuracies of AVS. These probably are due to superselective canalisation of adrenal veins, not draining venous effluent of the tumour producing aldosterone excess. In both cases, right SI were very high. These high ratios have been proposed as suggestive of very selective sampling, collecting blood of suppressed adrenal tissue, but not from the adenoma. Other possibility in the second case is anomalous drainage of pathologic tissue, by accessories veins not canulated in AVS, or an undetected extraadrenal source of aldosterone.

DOI: 10.1530/endoabs.37.EP34

EP35

The safety of steroid replacement and patient's knowledge

Ali Ahmed[1], Enis Mumdzic[2], Paul Wolfsan[3], Suha Atabani[4] & Mohammed Malik[4]
[1]Hull and East Yorkshire NHS Hospitals, Hull, UK; [2]Sheffield Teaching Hospitals, Sheffiled, UK; [3]Watford General Hospital, London, UK; [4]Christie Hospital, Manchester, UK.

Background
In steroid dependent patients the knowledge of steroid dose change during illness and stress is of paramount importance.
Objectives
i) To assess patient's knowledge of steroid management during acute illness and stressful condition. ii) To evaluate whether there is a relation between patient knowledge and admission with documented adrenal crisis. iii) To improve medical access to information about patients on steroid at Emergency Department.
Methods
i) Self-completed patient's questionnaire of 53 patients testing knowledge of on-going steroid treatment; self-held safety alert methods, dose adjustment during acute illness or surgery. ii) Review of patients' Clinical notes for documentation of advice given by the medical team. Also notes were reviewed for any documented hospital admissions in proven or suspected adrenal crisis over the study period.
Results
While vast majority of participants opted for continuing steroids during illness, only less than half answered they would double the dose. In case of recurrent vomiting; only 40% suggested the need for steroid injection. Half of participants were aware of the need for extra steroid during surgical procedure. Fifth of the total 53 participants did not carry a steroid card, and half did not wear any bracelet or have an emergency steroid injection.
Conclusion
This audit showed considerable gap in patients' knowledge and education. More effort is needed, probably using new methods. We introduced an electronic alert message for patients on steroid at the hospital emergency computer systems. We also suggested adopting a smart phone application advising patients about all aspects of steroid use.

DOI: 10.1530/endoabs.37.EP35

EP36

Pituitary macroadenoma with adrenocortical hypersecretion as the initial presentation of compensated adrenocortical failure

Serafino Lio & Monica Albin
Endocrine Unit, Ospedale Civile Oderzo-ASL n.9, Oderzo-TV, Italy.

Long-standing primary failure of pituitary-dependent endocrine glands may induce pituitary hyperplasia and adenoma both related to duration and severity of peripheral gland insufficiency, although the formation of an adenoma is rare. We report the case of an elderly man with pituitary macroadenoma but compensated adrenocortical failure. A 70-year-old man referred our centre in 2013 for headache and horizontal diplopia. MRI revealed pituitary macroadenoma (1.9$\times$ 1.1$\times$2.2 cm) with suprasellar extension, invasion of cavernous sinus, very close to the optic chiasm, localised T1 weighted-hyperintensity area suggestive of bleeding. Hormonal evaluation showed central hypothyroidism, hypogonadotropic hypogonadism, normal PRL, and GH/IGF1 serum levels, ACTH hypersecretion (fourfold above normal upper limit) with cortisol basal serum level at 6.1 μg/dl and peak level after corticotropin stimulation test (1 μg i.v.) at 21.2 μg/dl; renin and aldosterone serum levels were in the normal range; antibodies to adrenal cortex were negative, while those 21OH-Ab and very-long chain fatty acid unfortunately could not sampled; ANA-AMA-ADNA-ASMA-APCA, antiphosholipid Ab and TgAb-TPOAb were negative. Adrenal glands appeared normal at CT scan. Medical history was negative for tubercolosis. Weigt loss, hypotension, dehydratation, hyperpygmentation, fever, abdominal pain, as well as hyponatremia, hypo- or hyperkaliemia, hypo- or hypercalcaemia were not present; type 2 diabetes mellitus was diagnosed. Transphenoidal endoscopic excision was performed; the specimen was identified as adenoma at microscopical examination and immunocytochemical analysis showed diffuse immunoreactivity for ACTH, absent immunoreactivity for FSH, PRL, TSH, and GH; Ki67 $<$3% with p53 not expressed. In conclusion, this case shows that the formation of a pituitary adenoma is also possible in the forms yet compensated adrenal insufficiency; likely duration of adrenal failure, rather than the severity, may led a major role in the formation of the pituitary adenoma.

DOI: 10.1530/endoabs.37.EP36

EP37

Pregnancy-induced Cushing's syndrome

Corina Andreescu, Leo Hofland, Hans Hofland, Leendert Looijenga, Wouter de Herder & Richard Feelders
Erasmus Medical Center, Rotterdam, The Netherlands.

Cushing's syndrome (CS) during pregnancy is a rare metabolic condition with only a few cases reported in the literature. Misdiagnosis of CS is common because of the overlapping features of fatigue, weight gain, striae, and emotional changes that occur during normal pregnancy. The clinical presentation together with laboratory and imaging findings help to make a diagnosis. However, changes in maternal hormones and their binding proteins complicate assessment of the normal level of glucocorticoid hormones during gestation. CS during pregnancy is attributable most frequently to an adrenal adenoma and to a lesser degree to ACTH hypersecretion from a pituitary adenoma. Furthermore aberrant expression of various hormone receptors in the adrenal glands have been suggested to be involved in the pathogenesis of this condition, in particular the LH receptor. We investigated and treated three pregnant women with ACTH-independent CS and an adrenal tumor. After uncomplicated delivery patient 1 underwent *in vivo* testing for aberrant hormone receptor expression in the adenoma. Cortisol responses were found after administration of LHRH, human chorionic gonadotropin (hCG), TRH, glucagon, vasopressin, and a standard mixed meal. All patients were treated with laparoscopic adrenalectomy, after which signs and symptoms of hypercortisolism partially resolved. Adrenal tumour tissue of patients 1 and 2 showed positive immunohistochemical staining of LH receptors. Considering the cortisol responses to LHRH and hCG, and the development of CS during pregnancy in these patients, it is likely that ACTH-independent hypercortisolism was induced by the pregnancy-associated rise in hCG levels that activated aberrantly expressed LH receptors in the adrenal adenoma. Remarkably adrenal adenomas may simultaneously express multiple aberrant receptors and individual ligands may play a role in the regulation of cortisol production responsible for pregnancy-induced CS.

DOI: 10.1530/endoabs.37.EP37

EP38

Cardiovascular system abnormalities in patients with Cushing's syndrome

Tatiana Lebedeva, Victoria Pronina, Svetlana Fedorova, Alexander Dreval & Irina Komerdus
Moscow Regional Research Clinical Institute n.a.M.F. Vladimirsky, Moscow, Russia.

Background
Patients with Cushing's syndrome (CS) have a lot of complications due to chronic exposure of cortisol.
Aim
To reveal specific changes of cardiovascular system in patients with CS.
Material and methods
i) Six patients with CS (five females, one male, 47.1$\pm$1.5 years old), duration of CS 3.4$\pm$1.2 years, ii) 19 healthy patients (48.1$\pm$3.0 years old), and iii) ten patients with ischemic heart disease (IHD) (48.2$\pm$3.1 years old). Echocardiography; Holter monitoring (HM) and 24-h ambulatory blood pressure monitoring (ABPM) in bifunctional mode with program assessment of hemodynamic parameters and arterial stiffness (total peripheral vascular resistance (TPVR), index of arterial stiffness, heart rate variability, and circadian index) were assessed.
Results
Arterial hypertension was in all patients with CS. Mean daily BP 176$\pm$8/100$\pm$ 6 mmHg. Systolic pressure–time index 67.7$\pm$8.7%, diastolic pressure–time index 89.3$\pm$10.5%. 24-h rhythms of BP were disturbed in 67%, with prevalence of non-dippers and night-pickers in CS-patients. Strong correlations were found between cortisol levels (0800 and 2300 h) and systolic (SBP) and diastolic (DBP) day and night pressure (for 0800 h cortisol: SBP r=0.75, DBP r=0.8 (P=0.05); and 2300 h cortisol: SPB r=0.9, P=0.01; DPB r=0.95, P=0.05). Index of arterial stiffness was higher in patients with CS in comparison with patients with IHD. TPVR was increased in all patients with CS. Echocardiography: left atrial expansion in 67% of patients (4.2$\pm$1.1 cm), left ventricular hyperthrophy (in 50%), diastolic dysfunction (in 67%). Holter: mean heart rate (day 91.6$\pm$3.2 and

night 73.5±3.8) were higher in patients with CS than in other groups. 83.3% CS-patients had cardiac rhythm abnormalities that show predominance of activity of sympathetic nervous system.
Conclusion
All tests reveal significant changes in cardiovascular system in patients with CS with great predominance of activity of sympathetic nervous system. Index of arterial stiffness in patients with CS were higher than in patients with IHD, leads to higher risk of serious cardiovascular events in CS.

DOI: 10.1530/endoabs.37.EP38

EP39

Clinical management of adrenal insufficiency shows significant heterogeneity: data from the EU-AIR study

Robert D Murray[1], Bertil Ekman[2], Beverly A Jones[3], Claudio Marelli[4], Marcus Quinkler[5] & Pierre Zelissen[6]
[1]Leeds Teaching Hospitals NHS Trust, Leeds, UK; [2]Linköping University, Linköping, Sweden; [3]Shire PLC, Chesterbrook, Pennsylvania, USA; [4]Shire International GmbH, Zug, Switzerland; [5]Endokrinologie in Charlottenburg, Berlin, Germany; [6]University Medical Center Utrecht, Utrecht, The Netherlands.

Introduction
No consensus guidelines currently exist as to the optimal glucocorticoid regimen in adrenal insufficiency (AI). In clinical practice physicians utilise a number of different glucocorticoids, usually administered in several doses throughout the day.
Methods
The EU-AIR registry is a European multinational, multicentre, prospective, observational study sponsored by Shire inclusive of all patients with AI irrespective of aetiology. We analysed the baseline data of patients with primary (PAI) and secondary AI (SAI), excluding patients with CAH, to gain insight into AI current clinical management.
Results
As of 5th November 2014, 946 patients with AI (54.6±16.4 years, 510 (53.9%) F, BMI 28.0±5.5 kg/m^2, 310 (32.8%) PAI) were enrolled in to the study. Overall 91.8% of patients were receiving hydrocortisone (HC) as preferred glucocorticoid replacement, 6.8% prednisolone, 1.6% cortisone acetate, and 0.1% dexamethasone. For patients receiving HC, daily doses ranged from 5 to >45 mg. Most patients received 20–<25 mg (44.9%), with 24.3 and 16.0% receiving 15–<20 and 25–<30 mg respectively. 15.0% of patients were receiving HC doses ≥30 mg. Patients with PAI and SAI were receiving average HC doses of 23.3 and 19.3 mg respectively. HC was taken OD, BID, TID, and QID in 6.7, 52.1, 43.9, and 1.8% respectively. Patients with PAI were more likely to be receiving HC TID compared with those with SAI (56.9% vs 37.6%), who received their HC most frequently as a BID dosage (42.0% vs 56.9%). For patients receiving prednisolone daily doses ranged from <2 to >7.5 mg, with the majority (65.6%) receiving 5–<6 mg/day. A daily dose ≥6 mg was taken by 21.8%. Prednisolone was taken OD, BID, and TID in 73.4, 29.7, and 1.6% respectively.
Conclusions
We have demonstrated significant heterogeneity in the current management of AI in type of glucocorticoid, dosage, and frequency of administration. This likely reflects individualisation of regimes in the absence of robust data supportive of the optimal regimen for long-term outcomes.
Disclosure
This work was supported by Shire International GmbH.

DOI: 10.1530/endoabs.37.EP39

EP40

Postural orthostatic tachycardia syndrome unmasked by successful treatment of primary aldosteronism

Abbi Lulsegged, Nataliya Zuyeva & Nick Gall
Kings College Hospital NHS Foundation Trust, London, UK.

A 50-year-old woman was referred with a history of chronic, symptomatic hypokalaemia. She also had hypertension. There was no history of diarrhoea, increased bowel motions, vomiting, or laxatives/diuretic use. She was not diabetic and she did not have menopausal symptoms. Her mother had seven strokes and myocardial infarction. On examination weight is 69.9 kg, height 1.65 m, BP 163/99, pulse 70, heart sounds normal, and examination of the abdomen was unremarkable. ECG was normal. Despite taking potassium supplements, repeat blood tests showed sodium 148 mmol/l, potassium 3.3 mmol/l, magnesium 0.87, creatinine 56, and eGFR >90. Spot urine potassium 25 mmol/l. Primary aldosteronism was suspected. Her renin was undetectable (<1.1 ng/l) and serum aldosterone 772 pmol/l. Saline suppression test showed non-suppressible aldosterone levels. Glucocorticoid-remediable aldosteronism was excluded. MRI failed to show a adrenal lesion. Adrenal vein sampling however confirmed a unilateral, right sided adrenal source for the aldosterone excess and she underwent successful right adrenalectomy. Histology was supportive of the diagnosis. Shortly after the operation she started to experience significant postural dizziness. It was initially thought that this was due to relative suppression of aldosterone secretion by the contralateral gland and so fludrocortisone was started. A short Synacthen test excluded adrenal deficiency. She required increasing doses of fludrocortisone but despite this remained symptomatic. Additionally she experienced headaches, fatigue, cold intolerance, and breathlessness. Therefore a neurocardiogenic process was suspected and she was referred to cardiology. Tilt table test showed her heart rate gradually rose to 138 b.p.m. This was thought to be consistent with a POTs type response. Thus our patient had confirmed primary aldosteronism due to a adrenal adenoma, removal of which helped to unmask POTS. We hypothesise that the excess mineralocorticoid activity from the adenoma hyper secreting aldosterone helped to mask the neurocardiogenic process.

DOI: 10.1530/endoabs.37.EP40

EP41

Effect of stress-dosed hydrocortisone on physical capacity in patients with Addison's disease

Katerina Simunkova[1], Nevena Jovanovic[2], Marianne Oksnes[2], Kristian Lovas[1] & Eystein Sverre Husebye[1]
[1]Department of Clinical Science, University of Bergen, Bergen, Norway; [2]Department of Medicine, Haukeland University Hospital, Bergen, Norway.

The current conventional glucocorticoid (GC) replacement therapy in primary adrenal insufficiency (Addison's disease) and congenital adrenal hyperplasia (CAH) renders the cortisol levels unphysiological, resulting in very high levels alternating with almost undetectable levels of cortisol over the day. This reduces not merely the patient's quality of life but increases the patient's morbidity and mortality. The HPA axis is characterised by a dynamic circadian variation of cortisol with highest circulating levels in the early morning and a nadir late in the evening. The current therapeutical approach does not restore the circadian rhythm of cortisol. Recently replacement by continuous subcutaneous hydrocortisone infusion (CSHI) has been shown to mimic the circadian cortisol rhythm (Oksnes *et al*. 2014). CSHI treatment requires proper patient education and close monitoring during the first week of treatment until the correct dosage of hydrocortisone is defined. The starting dose is calculated according to body surface area and divided into four dosing intervals per day, corresponding with the circadian rhythm of cortisol. During the first day, the patient may report clinical signs of under-treatment; thus it is essential that the patient is thoroughly informed, and has the possibility to contact the physician directly if needed. The cortisol dosage should be double-checked in one week with serum cortisol, ACTH, cortisol saliva profile, and (possibly) 24 h urine collection, allowing for dose adjustment. In case of any illness the patient has to switch to the conventional tablet treatment and increase the dose of hydrocortisone according to the recommendation.
Disclosure
The work was supported by grant of Helse-Bergen Norway.

DOI: 10.1530/endoabs.37.EP41

EP42

Phenotypic characteristics of bilateral adrenal masses: about 34 cases

Nora Soumeya Fedala[1], Ali El Mahdi Haddam[2], Leyla Ahmed Ali[1], Mounia Benoumechiara[1], Farida Chentli[1] & Djamila Meskine[2]
[1]Bab El Oued Hospital, Algiers, Algeria; [2]Bologhine Hospital, Algiers, Algeria.

Introduction
Bilateral adrenal tumours are rare and account for 10–15% of adrenal lesions. They can be infectious, inflammatory, tumour, hémmoragiques, and genetic. The clinical and imaging used to guide diagnosis.
Aim
Assess clinical, etiologic, and therapeutic characteristics of bilateral adrenal masses.
Population and methodology
This is a retrospective study of the records of patients with bilateral adrenal masses collected over 26 years. All patients have benefited from a biological exploration (specific and non-specific) and oriented radiological investigation.
Results
34 patients were identified. The mean age at diagnosis was 45 ± 0.4 years. Sex ratio was 24 men/ten women. Diagnostic circumstances were: a chance discovery 11.8%, exploration of congenital adrenal hyperplasia (*n*: 44.11%), the staging of thyroid cancer: 17.64%, the exploration of a failure adrenal: 2.94%, 23.51% adrenergic signs. The etiological exploration revealed a bilateral phaeochromocytoma 10 (29.4%), adrenal metastases 8 (23.52%), nodular adrenal hyperplasia 15 (44.1%), and adrenal tuberculosis 1 (2.94%). The surgery was reported in 41.17% (all cases of phaeochromocytoma, nodular adrenal hyperplasia *n*: 3, suspicious adrenal masses of primitive non-Hodgkin lymphoma *n*: 1). The intervention was recused in other cases of adrenal metastases. Monitoring was instituted in other cases.
Discussion and conclusion
Bilateral adrenal masses are quite particular entity because of their rarity, their aetiologies and treatment. They must be characterised to be treated effectively. The improvement of radiological techniques and therapeutic modalities have enhanced their management.

DOI: 10.1530/endoabs.37.EP42

EP43

Impact of congenital adrenal hyperplasia and glucocorticoid treatment on the final size and gonadal function

Nora Soumeya Fedala[1], Ali El Mahdi Haddam[2], Leyla Ahmed Ali[1], Mounia Benoumechiara[1], Farida Chentli[2] & Djamila Meskine[1]
[1]Bab El Oued Hospital, Algiers, Algeria; [2]Bologhine Hospital, Algiers, Algeria.

Introduction
Congenital adrenal hyperplasia (CAH) are genetic diseases with a deficit of one of the enzymes of steroidogenesis (21 hydroxylase OH, 90%). The consequences of the adrenal hyperandrogenism that results are observed when the treatment is not undertaken precociously.
Aim
To study the impact of CAH and or treatment by glucocorticoids on the final size and gonadal function in girls.
Materials and methods
25 patients with CAH by 21-hydroxylase deficiency ($n=25$) or 11β-hydroxylase ($n=3$) with completed puberty were studied to assess the impact of affection and or glucocorticoid treatment on final height, pubertal development, and gonadal function in girls. Impact of congenital adrenal hyperplasia and glucocorticoid treatment on the final size and gonadal function.
Results
The mean age at diagnosis and initiation of treatment was 5 ± 2.4 years old (3–9). The mean final height was 150 ± 1.2 cm for girls ($n=18$) and 158 ± 2 cm for boys ($n=7$). 20% of patients have early puberty. In the remaining cases, delayed puberty was observed with a mean age of 14 ± 0.1 and 17 ± 1.2 years for onset of puberty and ménarchie in girls; 15 ± 1.4 years for boys. All girls had polycystic ovarian disease. 70% of patients had a persistent hyperandrogenism. 50% of patients were tightly controlled, 25% underdosed, and 25% overdosed.
Discussion and conclusion
Delayed diagnosis and poor compliance in our patients have resulted in a significant impact on growth in stature, pubertal development, and gonadal function. The introduction of routine neonatal screening for CAH in our country and more éfficace care of pathology will improve the functional prognosis of patients.

DOI: 10.1530/endoabs.37.EP43

EP44

Adrenal inclusions in congenital adrenal hyperplasia: clinical and progressive characteristics

Ali El Mahdi Haddam[1], Nora Soumeya Fedala[2], Leyla Ahmed Ali[2], Mounia Benoumechiara[2], Djamila Meskine[1] & Farida Chentli[2]
[1]Bologhine Hospital, Algiers, Algeria; [2]Bab El Oued Hospital, Algiers, Algeria.

Introduction
Intra-testicular adrenal inclusions (ISIT) are benign tumors made of ectopic adrenal cortex tissue hyper stimulated by ACTH in excess. All pathologies causing a rise ACTH levels may be associated with adrenal inclusions. They are found mainly in patients with congenital adrenal hyperplasia (CAH) of untreated or poorly treated.
Objective
Search the frequency of ISIT in CAH and clarify clinical and progressive characteristics.
Materials and methods
Forty patients with CAH responsible adrenal insufficiency (35 in 21 and one in five hydroxylase) underwent testicular echo-Doppler in search of ISIT. The volume of each testicle, the presence of ISIT, their size, echogenicity, and vascularity at diagnosis and during follow up.
Results
Adrenal inclusions were found in ten patients (25%). They were asymptomatic and bilateral in all case. Doppler ultrasound was suggestive in all patients (hilar localisation, mitigating but not calcified appearance, vascular architecture preserved). Partial regression after glucocorticoid treatment was noted in 95% of cases. In two cases the adrenal inclusion continued to grow requiring orchidéctomie. Histological study was in favour of a Leydig cell tumours.
Discussion and conclusion
ISIT are common in CAH (between 27 and 94%). Related to chronic stimulation by ACTH, they often reflect an insufficient suppressive treatment with glucocorticoid. The Doppler allows the characterisation. They must be systematically sought and monitored. They usually regress or stabilise with replacement glucocorticoid treatment. Sometimes they can grow, while raising the problem of the histological nature and risk of subfertility related to the mass effect of the ISIT and toxic effects of adrenal steroids and hypogonadotropic hypogonadism.

DOI: 10.1530/endoabs.37.EP44

EP45

X-linked adrenal hypoplasia congenita with a novel *DAX1* missense mutation

Fen-Yu Tseng[1], Yu-Ting Tseng[1], Shyang-Ron Shih[1] & Pei-Lung Chen[1,2]
[1]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [2]Department of Medical Genetics, National Taiwan University Hospital, Taipei, Taiwan.

Introduction
X-linked adrenal hypoplasia congenita (AHC) is a rare developmental disorder of the adrenal cortex. Adrenal insufficiency typically begins in infancy or in childhood. A few individuals present adrenal insufficiency in adulthood.
Case report
A 21-year-old man visited our endocrine out-patient clinic due to underdeveloped secondary sexual characteristics, which was found at physical examination for military service. Physical examination revealed small bilateral testes, sparse pubic, axillary hair, and a large arm span-to-height ratio. Besides, pigmentation in mouth, on palmar creases and joints were noted. Endocrine function evaluation showed high ACTH (>1250 pg/ml), low cortisol (5.37 μg/dl), low testosterone (0.541 ng/ml) with low FSH (4.79 mIU/ml), and low LH (2.77 mIU/ml). Peak LH level was 16.4 mIU/ml after LHRH stimulation, but response of FSH, LH, and testosterone to clomiphene was impaired. Thyroid function, HbA1c and serum electrolyte, plasma renin activity, and aldosterone levels were normal. Abdominal computed tomography scan revealed bilateral small adrenal glands. Brain MRI revealed no lesion at pituitary gland or hypothalamus. Adrenal hypoplasia congenital was suspected due to combined primary adrenal insufficiency and hypogonadotropic hypogonadism. Genetic study revealed a missense mutation (c.849G$>$C) in the *DAX-1* gene (dosage-sensitive sex reversal adrenal hypoplasia congenita, critical region on the X chromosome gene-1), which was transmitted from his mother.
Conclusion
DAX-1 gene deletions or mutations have been reported to be responsible for AHC. We report a case of AHC with adult-onset adrenal insufficiency, hypogonadotropic hypogonadism, and a novel missense mutation in the *DAX-1* gene.

DOI: 10.1530/endoabs.37.EP45

EP46

Adrenal insufficiency during prednisolone treatment: need for cortisol replacement strategies in patients on long-term low-dose glucocorticoid treatment?

Stina Willemoes Borresen[1], Bo Baslund[3], Marianne Klose[1], Åse Krogh Rasmussen[1], Lennart Friis-Hansen[2], Linda Hilsted[2], Henning Locht[4], Annette Hansen[5], Merete Lund Hetland[6] & Ulla Feldt-Rasmussen[1]
[1]Department of Endocrinology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [2]Department of Clinical Biochemistry, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [3]Department of Rheumatology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [4]Department of Rheumatology, Copenhagen University Hospital, Frederiksberg Hospital, Copenhagen, Denmark; [5]Department of Rheumatology, Copenhagen University Hospital, Gentofte Hospital, Copenhagen, Denmark; [6]Department of Rheumatology, Copenhagen University Hospital, Glostrup Hospital, Copenhagen, Denmark.

Background
Patients on long-term glucocorticoid treatment are at risk of adrenal insufficiency during glucocorticoid treatment. The side effect can occur during glucocorticoid treatment if there is a mismatch between glucocorticoid requirements and production/intake. High-dose glucocorticoid treatment is often sufficient to overcome most stressful situations. A low-dose of 5 mg prednisolone/day is however, equivalent to 20 mg hydrocortisone, a dose often used as basal glucocorticoid replacement in adrenal insufficiency. Contrary to patients in replacement therapy for adrenal insufficiency, patients treated with long-term low-dose glucocorticoids for various reasons are often not instructed in self-administration of supplemental doses in stressful situations.
Objective
We aimed to assess the prevalence of adrenal insufficiency in patients treated with 5 mg prednisolone/day.
Subjects and measures
As part of a larger study, 37 patients with rheumatoid arthritis (26 women, aged 36–85 years) treated with 5 mg prednisolone/day for at least 6 months (mean 108, range 6–336 months) had a 250 μg Synacthen test performed, after mean prednisolone pause of 47 h (range 36–96 h). P-cortisol was measured before and 30 min after Synacthen injection. Cut-off for normal adrenal function was 30 min P-cortisol >500 nmol/l as this is validated for our local cortisol assay. As a cut-off of 550 nmol/l is often used these data are also shown.
Results
Of the 37 patients 11 (30%) had an insufficient adrenal response to the Synacthen test. Using cut-off of 550 nmol/l 16/37 (43%) had adrenal insufficiency.
Conclusion
We found adrenal insufficiency in approximately one third of patients treated with 5 mg prednisolone/day. Since prednisolone treatment is often sustained for years in these patients, adrenal suppression is likely equally prolonged. Our findings raise the question whether a Synacthen test should be routinely performed in patients on long-term low-dose glucocorticoid treatment and insufficient patients handled with the same cortisol replacement strategies as other patients with verified adrenal insufficiency.
Disclosure
This study was supported by the Eva Maduras Foundation.

DOI: 10.1530/endoabs.37.EP46

EP47

A challenging case of paraneoplastic Cushing's syndrome

Adina Mazilu[1], Mona Gheorghiu[2], Madalina Musat[2], Aurelian-Emil Ranetti[1,2], Victor-Catalin Mazilu[1], Narcis Tanase[1], Razvan Petrescu[1], Adrian Ciuche[1], Augustin Tudose[1], Florina Vasilescu[1] & Carmen Ardeleanu[3]
[1]Central Military Emergency Hospital, Bucharest, Romania; [2]National Institute of Endocrinology 'C.I.Parhon', Bucharest, Romania; [3]Monza Hospital, Bucharest, Romania.

Introduction
Paraneoplastic Cushing' syndrome (CS) represents 5–10% of all CS and has a severe prognosis due to severe metabolic imbalance, denutrition, associated infections, and progression of tumoural underlying pathology.
A 67 years old woman presented with mental confusion, progressive weight loss, severe oedema and kypokalaemia, without typical features of Cushing or hyperpigmentation. Investigations revealed paraneoplastic Cushing's with ACTH 82.5 pg/ml, cortisol levels more than 63 μg/dl, probably produced by pulmonary tumour. Patient associated also empty sella syndrome with TSH and gonadotrophic insufficiency, left breast tumour, *Helicobacter pylori* gastritis, polinodular goitre, denutrition, and hepatic dysfunction. 99m-Tc tektrotyd scintigraphy was negative for pulmonary tumor, showing uptake in both adrenals and ileum. Patient needed 1200 mg/day ketoconazole and 200 mg/day of mifepristone in order to obtain normal cortisol levels and metabolic parameters. Owing to pulmonary sepsis and hepatic dysfunction we choose left adrenalectomy as first intervention, allowing reduction of ketoconazole to 600 mg/day and secondary left pulmonary lobe resection. Even if ketoconazole was stopped 1 day prior to adrenalectomy, patient developed adrenal insufficiency, needing noradrenaline support for 1 day and hydrocortisone replacement for 2 days. Histology exam showed benign bronchial carcinoid with ACTH staining and benign hyperplasia of left adrenal. Patient recovered almost completely. Mild hypokaliaemia and hypomagnesemia, even with oral supplementation, sartan therapy and normal levels of cortisol and ACTH persisted after surgery, probably due to severe deficit of intracellular compartment.
Conclusion
This case was difficult due to metabolic challenges, multiple associated pathology, lack of $SSTR_2$ and $SSTR_5$ receptors with negative scan, mild elevation of cromogranine A levels despite a typical bronchial carcinoid. Patient's sister was operated for adrenal adenoma confirmed on histology exam, her daughter had papillary thyroid cancer, but no MEN association was proven in this family.

DOI: 10.1530/endoabs.37.EP47

EP48

The treatment with 'dual release' hydrocortisone (DR-HC) in congenital adrenal hyperplasia: short-term (6 months) and long-term (12 months) follow-up after the switch from conventional glucocorticoids to DR-HC

Chiara Simeoli, Maria Cristina De Martino, Davide Iacuaniello, Teresa Mannarino, Alessia Cozzolino, Monica De Leo, Claudia Pivonello, Mariarosaria Negri, Cristina De Angelis, Annamaria Colao & Rosario Pivonello
Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, Università 'Federico II' di Napoli, Naples, Italy.

In patients with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency, life-long glucocorticoid (GC) treatment is often required to replace cortisol deficiency and to avoid the ACTH-dependent androgen levels increase. However, in these patients, the multiple daily doses required with conventional GCs can cause cortisol overexposure, leading to an increased risk of metabolic syndrome (MS), an impaired quality of life (QoL), and poor treatment compliance (TC). The current study aimed at investigating the impact of the switch from twice or thrice daily conventional GCs to once daily 'dual release' hydrocortisone (DR-HC) on metabolic and hormonal profile, QoL, depression status (DS), and TC in a cohort of patients with CAH. Twenty-three CAH patients (16F, 7M, 20–38 years), treated with HC (10–40 mg/day) or prednisone (6.25–12.5 mg/day) for at least 12 months, switched to DR-HC (10–40 mg/day) entered the study and were evaluated before and after 6–12 months of DR-HC. Metabolic and hormonal parameters were measured using routine assays and the MS was evaluated according with IDF criteria. QoL, DS, and TC were assessed using AddiQoL Questionnaire, Beck Depression Inventory II, and Morisky 8-items medication Adherence Questionnaire respectively. The change in metabolic and hormonal parameters in the same cohort of patients along the year between baseline and 12 months before the switch, while patients stably performed conventional GCs, was used as control. At 6-month follow-up, fasting plasma glucose ($P=0.003$) was significantly reduced, whereas at 12-month follow-up HDL ($P=0.000$) and LDL-cholesterol levels ($P=0.024$) were significantly improved as compared with baseline. A clear diagnosis of MS was performed in one patient at baseline, but this patient displayed no criteria for this diagnosis after 6 and 12 months. No significant change in morning plasma ACTH, UFC, and serum aldosterone, 17-OH progesterone, testosterone, DHEA-S, and androstenedione levels were observed and no clinical worsening of symptoms and signs related to hyperandrogenism were reported. Excluding from the analysis the four patients treated with prednisone at baseline, a significant increase in morning serum cortisol levels was registered after 6 months ($P=0.016$) but it was not confirmed after 12 months. Despite the unchanged fludrocortisone doses, both in the entire cohort ($P=0.002$) and in the subgroup of patients with salt wasting form ($P=0.005$) a significant decrease in renin levels was reported at 6-month follow-up, but it was not confirmed at 12-month follow-up. As control, no significant difference was observed in metabolic and hormonal parameters in the same cohort of patients between baseline and 12 months before the switch. Additionally, DS improved both after 6 months ($P=0.04$) and 12 months ($P=0.07$) whereas TC significantly, progressively, improved after 6 months ($P=0.009$) and after 12 months ($P=0.000$). In conclusion, the switch from conventional GCs to

DR-HC significantly improves MS, DS, and TC, maintaining an optimal hormone control in patients with CAH due to 21-hydroxylase deficiency.

DOI: 10.1530/endoabs.37.EP48

EP49

The effect of oxidative stress to cardiovascular risk profile among non-functional adrenal incidentaloma patients

Hanife Bolat[1], Kamile Gul[2], Gulizar Sokmen[3], Murat Sahin[2], Ergul Kurutas[4], Ayten Oguz[2], Abdullah Sokmen[3], Dilek Tuzun[2], Safiye Seyma Taner[4] & Omer Faruk Akgul[1]
[1]Department of Internal Medicine, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey; [2]Department of Endocrinology and Metabolism, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey; [3]Department of Cardiology, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey; [4]Department of Biochemistry, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey.

Aim
In this study our aim was to investigate the effects of non-functional adrenal incidentalomas to cardio-metabolic risk factors and endothelial function.
Materials and methods
Our study involved 30 patients with non-functional adrenal incidentaloma (patient group), and two control groups without adrenal incidentaloma (control group 1 involved 26 patients have DM and/or HT and control group 2 involved 24 healthy control). Metabolic parameters (fasting blood glucose and lipid profile), hsCRP, oxidative stress parameters such as malondialdehyde (MDA), nitric oxide (NO), nitrotyrosine (3-NTx), and antioxidants parameters such as catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and melatonin were evaluated in all participants.
Results
When we compared the patient and control groups; hsCRP, oxidative stress parameters (MDA, NO, and 3-NTx) were significantly higher in patient group ($P<0.001$) but antioxidant parameters such as melatonin, GPx, and SOD were significantly lower in patient group ($P<0.001$). Cortisol levels after 1 mg dexamethasone suppression test were significantly higher in patient group ($P<0,01$). There was a significant positive correlation between cortisol levels after 1 mg dexamethasone suppression test and hsCRP, MDA, NO, and 3-NTx levels ($P<0.05$) and there was a significant negative correlation between cortisol levels after 1 mg dexamethasone suppression test and melatonin, GPx, and SOD levels ($P<0.001$).
Conclusion
Adrenal incidentalomas are usually thought to be benign and asymptomatic lesions. But recent studies reported that autonomic cortisol secretion was higher than expected in incidentalomas and they have increased cardiovascular risk. But it is not clear whether adrenal incidentalomas increase the atherosclerosis and cardio-metabolic risk or this adrenal tumours mostly seen in patients that have cardio-metabolic risks. According to the data obtained from this study; we suggest that the oxidative stress increases markedly in the patients with non-functional adrenal incidentalomas, so this process leads the atherosclerosis eventually. Moreover we showed that non-functional adrenal incidentaloma patients have higher cortisol levels when compared both with healthy controls and patients that have cardiovascular risk factors. Therefore we suggest to consider the factors that mentioned above when evaluating the non-functional adrenal incidentaloma patients.

DOI: 10.1530/endoabs.37.EP49

EP50

Malignant phaeochromocytoma: about seven observations

Mounia Benoumechiara[1], Nora Soumeya Fedala[2], Ali El Mahdi Haddam[2], Leyla Ahmed Ali[1], Farida Chentli[1] & Djamila Meskine[2]
[1]Bab El Oued Hospital, Algiers, Algeria; [2]Bologhine Hospital, Algiers, Algeria.

Introduction
Malignant phaeochromocytomas are rare tumours, developed at the medulla and paraganglia. Their diagnosis is established by the presence of metastases of organs devoid of chromaffin tissue or by the appearance of neoplastic recurrence. They are characterized by a morbidity and mortality due to the effects of uncontrolled and important hypersecretion cathécolaminergique and resistance to conventional cancer treatments.
Aim
Report the observations of seven cases observed in 26 years.
Materials and methods
Seven patients with malignant phaeochromocytomas were treated in our department. Three were males and four females and their ages ranged between 17 and 45 years old. The circumstances discoveries were adrenergic signs and severe hypertension in all cases. Hormonal balance showed very high levels of metanephrine: 20 ± 1.4 (16–22) and CT + MRI showed a large and characteristic adrenal mass: 12.6 ± 1.2 cm (14–9.6). Malignancy was confirmed by the presence of metastasis at diagnosis in five cases and in the developments in the rest of the cases. Evolution was marked a year and a half after on average (after surgery and chemotherapy) by a normalisation of blood pressure, methoxylated derivatives in five patients. Two deaths occurred after the first course of chemotherapy.
Discussion and conclusion
Surgery of malignant phaeochromocytoma, even at metastatic stage increases survival. Chemo radiotherapy and MIBG are part of the therapeutic arsenal. The management of these patients requires a multidisciplinary follow up (surgeon, oncologist, endocrinologist, histopathologist, and geneticist).

DOI: 10.1530/endoabs.37.EP50

EP51

Comparison of 17-OH progesterone response to various dose of tetracosactide

Mikuláš Kosák[1], Michaela Duškova[2], Katerina Šimunková[1,2], Václav Hána[1], Michal Kršek[1], Hana Jandíková[2], Hana Pospíšilová[2], Monika Šrámková[2], Marta Velíková[2] & Luboslav Stárka[2]
[1]3rd Department of Medicine, General University Hospital and First Faculty of Medicine, Charles University, Prague, Czech Republic; [2]Institute of Endocrinology, Prague, Czech Republic.

ACTH test is widely accepted as diagnostic tool in suspicion on peripheral as well as on central hypocorticism. The optimal dose of tetracosactide for determination of hypocorticism is still matter of debate. The 250 μg as a standard dose of tetracosactide has been approved for diagnosis of congenital adrenal hyperplasia (CAH) many years ago. Moreover, current limited availability of tetracosactide and its increased financial cost on the market raised the question whether the lower dose of tetracosactide for diagnosis of CAH may be sufficient stimulation.
Aims
To compare response of 17-OH progesterone (17-OHP) to various doses of tetracosactide in healthy volunteers.
Methods
In ten healthy volunteers (four males, median 42 years) with normal adrenal function (based on clinical and biochemical evaluation) the ACTH tests with i.v. administration of 250 μg (HDST), 10 μg (MDST), and 1 μg (LDST) tetracosactide were performed.
Results
Similar response in 17-OHP levels in all three variants of the test was observed. Median 17-OHP levels 30 min after the tetracosactide administration were 6.62, 6.62, and 5.68 nmol/l for HDST, MDST, and LDST respectively. 60 min after the administration the median levels were 6.93, 5.91, and 4.70 nmol/l.
Conclusion
Our data support the hypothesis of ACTH test reliability for the diagnosis of CAH in all variants with lower doses of ACTH compared to standard dose. Further confirmation of our observation in patients with known non-classical form of CAH would be appropriate.
Disclosure
This work was supported by grant number NT 11277-6 of the IGA MZCR.

DOI: 10.1530/endoabs.37.EP51

EP52

Functional oncocytic adrenocortical tumour: a case report

Murat Sahin[1], Dilek Tuzun[1], Ayten Oguz[1], Mehmet Fatih Yuzbasioglu[2], Hamide Sayar[3], Hakan Demir[4] & Kamile Gul[1]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey; [2]Department of General Surgery, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey; [3]Department of Pathology, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey; [4]Department of Internal Medicine, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey.

Introduction
Adrenocortical oncocytomas are rare seen tumours. Most of these tumours are benign and non-functioning. We present here a case of oncocytic adrenocortical tumour, detected incidentally, presented with Cushing's syndrome.
Case
A 41-year-old male patient, while investigating for abdominal pain, bilateral adrenal masses were detected in abdominal ultrasonography and was admitted to Endocrinology Clinic. He had no history of hypertension. Physical examination revealed, a pulse rate of 80 beats/min and a blood pressure of 180/90 mmHg. Patient had typical cushingoid appearance including a plethoric moon face, truncal and centripetal obesity and abdominal cutaneous striae. In his laboratory investigations; glucose level was 97 mg/dl, ALT 80 U/l (30–65), cortisol 18.47 μg/dl (5–23), DHEAS >1000 μg/dl (35–560), and ACTH <5 pg/ml (9–52). In the 24-h urine metanephrine level, normetanefrin and plasma aldosteron concentration, plasma renin concentration were normal. Other biochemical blood test results were within normal ranges. The plasma cortisol level was 24 μg/dl after 1 mg overnight, 22 μg/dl after 2 days 2 mg dexamethasone suppression test, and midnight cortisol was 14 μg/dl. According to these findings Cushing's syndrome was considered. Surrenal magnetic resonance imaging (MRI) that showed bilateral adrenal adenomas that were 35×32 mm in size in the right and 78×64 mm in the left adrenal gland, isointense in T1A and T2 and included cystic regions. Left adrenalectomy was performed to the patient. The postoperative histopathological diagnosis was borderline oncocytic adrenocortical tumour with myelolipoma foci and Ki-67 proliferation index was under 1%. The patient is still under follow-up at our clinic with the replacement therapy of steroid.
Conclusion
The incidence of adrenal incidentaloma is increasing according to technological development and frequency of radiological imaging. Adrenocortical oncocytomas are rare seen tumours. Most of these tumours are benign and non-functioning. Some of that tumours are malign and while the others are borderline. Oncocytic neoplasms microscopically consist of so called oncocytes, large cells with rich eosinophilic granulations due to the high concentration of mitochondria. We present a case with oncocytic adrenocortical tumour presented with Cushing's syndrome because it is seen rare.

DOI: 10.1530/endoabs.37.EP52

EP53

Beneficial effects of replacement therapy with modified-release hydrocortisone in patients with adrenal insufficiency

Valentina Morelli[1], Erika Messina[2], Marco Mendola[3], Elisa Cairoli[1], Bruno Ambrosi[3], Salvatore Cannavò[2], Iacopo Chiodini[1] & Anna Spada[1]
[1]Unit of Endocrinology and Mebabolic Diseases, Fondazione IRCCS Cà Granda-Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; [2]Unit of Endocrinology, Azienda Ospedaliera Universitaria Policlinico Gaetano Martino, University of Messina, Messina, Italy; [3]Endocrinology and Diabetology Unit, IRCCS Policlinico San Donato, San Donato Milanese, University of Milan, Milan, Italy.

Introduction
The classical replacement therapy for hypoadrenalism may expose patients to non-physiologic glucocorticoids levels with negative metabolic consequences. Up to now, one study demonstrated that, as compared to the classical treatment, a modified-release hydrocortisone (MRH), improves weight, blood pressure, glycaemic control and QoL in a 3-month follow-up period. Few data are available on the long-term persistence of these benefits.
Design/methods
Ten patients with Addison's disease and seven with central hypocortisolism (mean±s.d., age 50.8±10.7 years, BMI 27.9±7.0 kg/m^2, 9M/8F) were enrolled in three Italian Endocrine Units. 12 patients were treated with cortisone acetate (30.2±10.9 mg/day), five patients with hydrocortisone (25±5 mg/day), with an inadequate control of the disease. 80% of patients reported fatigue. In all patients, after baseline evaluations, the classical therapy was replaced with MRH (20.3±1.2 mg/day). At 1, 3, 6, and 12 months after the therapy modification (mean follow-up: 8.8±4.2 months) we evaluated parameters of adrenal function, BMI, blood pressure, HbA1c levels, and symptoms of over- or under-treatment.
Results
MRH caused higher morning cortisol levels than the classical therapy (after 12 months: 20.7±6.5 μg/dl vs 13.2±3.5 μg/dl, $P=0.012$), but comparable UFC values (after 12 months: 29.1±14 μg/24 h vs 24.1±9.5 μg/24 h, $P=0.299$), confirmed at each evaluation. In Addisonian patients MRH did not influence ACTH levels over time (after 12 months: 175.8±215 pg/ml vs 150.6±157 pg/ml, $P=0.781$). Paired sample *T*-test showed that metabolic parameters did not change after 1, 3, and 6 months. The ten patients that completed the 12 months follow-up, showed a reduction of BMI (29.2±5.8 vs 28.3±5.2, $P=0.027$) and systolic (126±18 mmHg vs 115±18 mmHg, $P=0.03$) blood pressure, while HbA1c decreased in the two diabetic patients (8.1±0.7% vs 5.9±1.1%). 60% of patients showed an improvement of fatigue after 6 months ($P=0.023$) that persisted at 12 months.
Conclusion
In patients with hypoadrenalism, a 12 months treatment with MRH seems to improve some metabolic parameter and to reduce weakness.

DOI: 10.1530/endoabs.37.EP53

EP54

A phase 1, randomised, open-label, four-period crossover, single-dose study to evaluate the pharmacokinetics of hydrocortisone modified release tablets

Gudmundur Johannsson[1], Hans Lennernäs[2], Claudio Marelli[3], Kevin Rockich[4] & Stanko Skrtic[1]
[1]Department of Endocrinology, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gotheburg, Sweden; [2]Department of Pharmacy, Uppsala University, Uppsala, Sweden; [3]Shire, Zug, Switzerland; [4]Shire PLC, Chesterbrook, Pennsylvania, USA.

Novel biopharmaceutical techniques have allowed the development of a hydrocortisone modified release (MR) tablet (once-daily administration for replacement therapy in adrenal insufficiency) mimicking more closely the physiological serum cortisol profile. Robust bioavailability is needed to secure this new treatment safety.
Aims
To compare single-dose pharmacokinetics (PK) of MR tablets manufactured at two different sites by assessing intra-subject variability (dose range: 5–20 mg).
Methods
Thirty-two healthy men and women (20–55 years; BMI: 18–30 kg/m^2) were enrolled into a randomized, open-label, four-period crossover, single-dose PK study with collection of baseline 24 h endogenous cortisol secretion. During four periods 5, 15, 20 (new manufacturing site R), and 20 mg (reference site G) were administered orally at 0800 h after overnight fast. Endogenous cortisol secretion during PK sampling was suppressed using dexamethasone. PK parameters were determined using non-compartmental analysis. Plasma cortisol was measured using LC–MS/MS.
Results
Within-individual comparison between the endogenous profile and the 20 mg tablet showed hydrocortisone treatment provided higher than endogenous concentrations 0–4 h post-dose and similar concentrations 5–15 h post-dose. Mean hydrocortisone *C*max (s.d.) was 82.0 (18.2), 148.8 (29.3), 177.1 (25.5), and 178.0 (28.1) ng/ml and mean AUC∞ was 523.8 (128.0), 1024.5 (158.1), 1178.2 (222.2), and 1191.4 (190.9) h×ng/ml for 5, 15, 20 mg R treatments, and 20 mg G treatment respectively. Bioequivalence, defined as the 90% CI being within the 80 125% limits, was demonstrated. Within-subject variability was below 15% for all examined PK parameters for the 20 mg R and G MR tablet oral administration. Exposure PK parameters were found to be less than dose proportional, i.e. AUC∞ with a 0.78 slope (95% CI: 0.70–0.85) in the 5–20 mg dose range.
Conclusions
Once daily MR hydrocortisone demonstrates a physiological cortisol exposure during the day. Within-individual day-to-day PK variability is very low underpinning product safety for replacement therapy. Hydrocortisone PK is less than dose proportional, an important PK property of oral hydrocortisone that should be considered in the intercurrent illness management of adrenal insufficiency.
Disclosure
This work was supported by Shire.

DOI: 10.1530/endoabs.37.EP54

EP55

Rare case of ectopic ACTH secreting tumour causing cyclical Cushing's syndrome

Jayashekara Acharya, Sriranganath Akavarapu, Ali Abbara, Valsalakumari Parvathy & J F Todd
Hammersmith Hospital, London, UK.

We are reporting a rare case of ectopic ACTH secreting tumour causing cyclical Cushing's syndrome. A 63-year-old lady presented in March 2013 with tiredness and bilateral leg swelling and weakness associated with easy bruising. She was admitted to local hospital in April 2013 with worsening proximal myopathy and

peripheral oedema. Her midnight cortisol was elevated at 1710 nmol/l. ACTH 610 mU/l, prolactin 476 mU/l, GH 0.21 IU/l, TSH 0.73 mU/l, free T_4 of 11.0 pmol/l, LH 0.5 IU/l, and FSH 1.5 IU/l. A cortisol day curve on metyrapone 500 mg tds showed elevated cortisol of 507, 989, and 273 nmol/l at 0900, 1200, and 1800 h. MRI pituitary showed normal appearance of the pituitary gland. Abdominal CT scan revealed bilateral adrenal hyperplasia. Despite metyrapone 250 mg tds her cortisol levels remained elevated (200–400 nmol/l). Metyrapone was stopped a week before (30th May) bilateral inferior petrosal sinus sampling. Results were suggestive of central ACTH-dependent Cushing's syndrome. However her cortisol levels normalised post IPSS, without reintroduction of metyrapone (between 125 and 250 nmol/l). Her midnight cortisol was low at 41 nmol/l and ACTH of 43 mU/l. She was discharged home as her symptoms resolved and biochemistry normalised post discharge insulin stress test in August showed suboptimal cortisol response of 409 nmol/l. She was started on hydrocortisone replacement. Her symptoms relapsed in September 2013 with midnight cortisol of 1400 nmol/l with ACTH of 431 nmol/l consistent with relapsed Cushing's syndrome. She failed to suppress on a low dose dexamethasone test and she was restarted on metyraone to improve her symptoms. She underwent Gallium DOTATATE scan, which showed right lower lobe Gallium avid lesion. Repeat IPSS done in September did not show any central gradient confirming an ectopic source. She underwent surgical excision of lung lesion in December 2013. Histology was consistent with neuro endocrine tumour (Ki67 $<3\%$). Her symptoms improved after surgery and her cortisol levels fell. She was started on hydrocortisone after she failed on short Synacthen test.

Conclusion

Cyclical Cushing's syndrome is a rare cause of hypercortisolism. Corticotroph adenoma is the most common cause. Cyclical Cushing's syndrome due to ectopic ACTH is extremely difficult to diagnose due to fluctuating clinical picture and biochemistry. In suspected cases specific biochemical and imaging investigation for neuroendocrine tumour is required.

DOI: 10.1530/endoabs.37.EP55

EP56

Review of clinical presentation of primary hyperaldosteronism and identify unique features in our cohort

Daphne Lee, Shaikh A K K Abdul Shakoor, Uei Pua, Daniel Wong & Lawrence Quek
Tan Tock Seng Hospital, Singapore, Singapore.

Aim

Review of clinical presentation of primary hyperaldosteronism (PHA) and identify unique features in our cohort.

Method

Patients with PHA were identified from patients who underwent adrenal vein sampling (AVS) at our centre until October 2014.

Results

45 PHA patients (32 males, mean age of 50 years, 33 older than 45 years) were identified after confirmation with high aldosterone:renin ratio >15 and/or positive saline suppression test. All had hypertension and 41/45 (91.1%) presented with hypokalaemia. CT adrenal findings were; 31/45 (68.9%) unilateral nodule (one had two nodules unilaterally), 5/45 (11.1%) bilateral nodules, 7/45 no nodules, 1/45 bilateral bulky adrenals, and 1/45 left adrenal limb thickening. The mean tumour size on CT was 1.41 (0.7–2.3) cm. All underwent AVS (four had repeat investigation). Based on biochemical criteria, 61% (30/49) of cases were successfully cannulated bilaterally. Final diagnosis of PHA was established after evaluating both CT and AVS findings (ratio of higher over lower aldosterone/cortisol of >4 for aldosterone producing adenoma (APA) and <3 for bilateral adrenal hyperplasia (BAH)) by the primary clinician: 18 had APA, 16 had BAH, and 11 were inconclusive. 17/45 (37.8%) patients underwent surgery (all confirmed as APA on histology). After surgery, hypokalemia normalised in all, 15/17 (88.2%) BP improved and 3/17 (17.6%) were cured of hypertension. Among 27 patients treated medically, 25/27 (92.6%) had normalisation of potassium, 25/27 (92.6%) BP improved and 2/27 (7.4%) were cured of hypertension. One patient declined treatment.

Discussion

The prevalence of BAH is higher in our cohort compared to reported series but this could be due to selection of cases through AVS procedure as some cases of APA may have been missed because they did not undergo AVS. The prevalence of inconclusive diagnosis after AVS was higher, which could be related to the expertise in our centre.

DOI: 10.1530/endoabs.37.EP56

EP57

To identify usefulness of adrenal vein sampling in clinical management of primary hyperaldosteronism

Daphne Lee, Shaikh A K K Abdul Shakoor, Uei Pua, Daniel Wong & Lawrence Quek
Tan Tock Seng Hospital, Singapore, Singapore.

Aim

To identify usefulness of adrenal vein sampling (AVS) in clinical management of primary hyperaldosteronism (PHA).

Method

Biochemical and radiological review (by two independent radiologists) of 48 AVS in 45 patients with PHA who underwent CT adrenals/AVS.

Results

CT adrenal findings were: 31/45 (68.9%) unilateral nodule (one had two nodules unilaterally), 5/45 (11.1%) bilateral nodules, 7/45 no nodules, 1/45 bilateral bulky adrenals, and 1/45 left adrenal limb thickening. Selectivity index (adrenal vein cortisol/infra adrenal IVC cortisol) >5 and lateralisation index (ratio of higher over lower aldosterone/cortisol ratio) >4 for aldosterone producing adenoma (APA) and <3 for bilateral adrenal hyperplasia (BAH) were used for AVS. Based on radiological review, 29% (14/48) of cases were cannulated bilaterally. Between radiologists, there was discordance in opinion regarding successful cannulation; 48% (23/48) right side vs 8.3% (4/48) left side. There was better agreement between radiological review and biochemical criteria on the left side (37/48 vs 18/48). Based on biochemical criteria, 59% (29/48) of cases were cannulated bilaterally; 14/29 APA, 12/29 BAH, and 3/29 inconclusive. Clinical conclusion in the remaining 19 unsuccessful cases were; 4/19 APA on secondary criteria (non-suppression of aldosterone on contralateral side) and 3/19 BAH and 12/19 inconclusive. AVS finding in patients with unilateral nodule on CT; 13/31 (42%) APA on same side as CT (four using secondary criteria), 10/31 (32.2%) BAH, and 8/31 inconclusive. On the contrary, AVS lateralised to one side in four patients with bilateral nodules and one with normal CT. Nodules >1.5 cm predicted lateralisation to the same side in AVS, with a positive predictive value of 70% compared to nodules ≤ 1.5 cm on CT.

Conclusion

AVS provided additional information over CT in the management of PHA; AVS helped to save 11 patients from unnecessary surgery and directed five patients who would otherwise have been treated medically, for curative surgery.

DOI: 10.1530/endoabs.37.EP57

EP58

Diagnosis of Cushing's syndrome using scalp hair cortisol

Vincent L Wester[1], Jan W Koper[1], Erica L T van den Akker[2], Yolanda B de Rijke[3], Laura Manenschijn[1], Richard A Feelders[1] & Elisabeth F C van Rossum[1]
[1]Department of Internal Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; [2]Department of Pediatrics, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; [3]Department of Clinical Chemistry, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands.

Background

Endogenous Cushing's syndrome (CS) is caused by overproduction of cortisol. Current first-line screening tests for CS can produce false positive results due to medication use and stress, rely heavily on patient adherence to sampling instructions, and only measure short-term cortisol exposure which limits sensitivity. In general multiple tests are required to establish a diagnosis. Hair cortisol concentrations (HCC) offer a minimally invasive way to measure long-term cortisol exposure over months of time, and are a promising additional screening tool for CS. In addition, HCC can be used to create retrospective timelines of cortisol exposure.

Methods

We collected scalp hair from patients suspected of CS in a single academic medical center, and in healthy controls. HCC were measured using ELISA. Receiver operator curve (ROC) analysis was used to determine the optimal cut-off for CS.

Results

HCC levels were available in 35 patients with CS, 20 patients in whom the diagnosis CS could be rejected during diagnostic work-up (non-CS patients), and 174 healthy controls. CS patients had higher HCC than non-CS patients and healthy controls (157.6 vs 9.7 and 8.4 pg/mg, respectively, $P<0.001$). At a cut-off of 31.1 pg/mg, HCC could differentiate between CS patients and healthy controls with a sensitivity of 94% and a specificity of 90%. With non-CS patients as a reference, sensitivity and specificity remained similar (94 and 90%

respectively). As expected, HCC was higher in ectopic ACTH secretion than in pituitary or adrenal CS (661.1 vs 105.9 and 123.0 pg/mg, respectively, $P < 0.05$). Retrospective timelines of HCC corresponded well with clinical course in CS.
Conclusion
Analysis of cortisol in a single scalp hair sample offers diagnostic accuracy for CS similar to current first line tests and a collection procedure which is highly convenient for clinical practice, and therefore seems a valuable tool in the diagnosis of CS.
Disclosure
This work was supported by an Erasmus MC fellowship grant and The Netherlands Organization for Scientific Research (NWO) grant number 916.96.069.

DOI: 10.1530/endoabs.37.EP58

EP59

Role for ^{131}I-6β-iodomethyl-norcholesterol scintigraphy in subclinical Cushing's syndrome with bilateral adrenal lesions

Daniela Guelho[1], Rui Ferreira[2], Isabel Paiva[1], Ana Paula Moreira[2], Carolina Moreno[1], Luis Cardoso[1], Nuno Vicente[1], Diana Martins[1], Diana Oliveira[1], Margarida Balsa[3], Gracinda Costa[2] & Francisco Carrilho[1]
[1]Endocrinology, Diabetes and Metabolism Department, Coimbra Hospital and University Centre, Coimbra, Portugal; [2]Nuclear Medicine Department, Coimbra Hospital and University Centre, Coimbra, Portugal; [3]Endocrinology, Diabetes and Nutrition Department, Baixo Vouga Hospital Centre, Aveiro, Portugal.

Introduction
Subclinical Cushing's syndrome (SCS) is the most frequent endocrine dysfunction found in adrenal incidentalomas. Although adrenalectomy constitutes a therapeutic option for selected cases, the presence of bilateral tumours can difficult the surgical decision.
Objective
Evaluate the utility of ^{131}I-6β-iodomethyl-19-norcholesterol scintigraphy in SCS with bilateral adrenal tumours.
Methods
Retrospective analysis of all patients with SCS and bilateral adrenal lesions submitted to ^{131}I-6β-iodomethyl-19-norcholesterol scintigraphy in our Nuclear Medicine Department. Following suppression with dexamethasone, planar thoracoabdominal scintigraphy, and single photon emission computed tomography (SPECT/CT) images were obtained at 3rd, 5th, and 7th days after i.v. administration of 1 mCi of ^{131}I-6β-iodomethyl-19-norcholesterol.
Results
Five scintigraphy were performed in four women, aged 57.5 years (46–67 years), with SCS and bilateral incidentalomas identified by abdominal CT: at right with a median diameter of 19 mm (17–35 mm) and at left with 18 mm (7–28 mm). All patients presented osteoporosis; two had dyslipidaemia and two had arterial hypertension. Two patients showed radiopharmaceutical uptake at right adrenal with non-visualisation of contralateral gland: both were proposed to adrenalectomy. Histopathological study confirmed the adrenal cortical adenoma. After surgery, a significant improvement of their comorbidities was observed with reduction of anti-hypertensive drugs. Other patient exhibited symmetrical uptake and was maintained on medical treatment. In the fourth patient, both the first scintigraphy and adrenal vein sampling were inconclusive. However, after a second scintigraphy that suggested a hyperfunctioning right adenoma, she was submitted adrenalectomy that confirmed the lesion.
Conclusions
This work suggests a high resolution of the adrenal ^{131}I-6β-iodomethyl-19-norcholesterol scintigraphy, providing a more precise picture of functional structural lesions that crosses the information obtained by CT and hormonal assays. In these patients enabled a more targeted surgical approach, preserving the other adrenal and improving their comorbidities.

DOI: 10.1530/endoabs.37.EP59

EP60

Diagnostic pitfalls of Cushing's syndrome without specific clinical signs among patients with obesity

Nalalia Volkova, Maria Porksheyan & Lilia Ganenko
Rostov State Medical University, Rostov-on-Don, Russia.

Introduction
Prevalence of CS without specific signs is thought to be high, which might be an indication for its general screening. However, conclusive data about its diagnostics is absent.
Design
189 overweight patients were studied. Nobody had clinical evidence of hypercortisolism. Diagnostic of CS was 1-mg overnight dexamethasone suppression test (1-mg DST; cut off 50 nmol/l) as a screening; midnight plasma cortisol (MPC) (<207 nmol/l) and 24-h urinary free cortisol (UFC) (<180 μg/24 h) as a confirmatory tests; morning plasma ACTH (5–46 pg/ml), 8-mg DST and imaging studies as topical diagnostics.
Results
Among 189 patients 166 were excluded to have CS according to results of DST 1 mg (<50 nmol/l). 23 had impaired result of 1-mg DST. Among these 23 patients there were diagnosed four cases of corticotropinomas, two corticosteromas. Other 17 patients were excluded to have CS by long-term follow-up and, therefore, they had falsely positive results of confirmatory tests. The diagnostic characteristic of MPC and UFC with established cut off were calculated: MPC – Sen 83.33% (95% CI 35.88–99.58), Sp 63.64% (95% CI 30.79–89.07), LR+ 2.29, LR− 0.26, DOR 8.75 (95% CI 0.73–103.82), UFC – 83.33% (95% CI 35.88–99.58), Sp 18.18% (95% CI 2.28–51.78), LR+ 1.02, LR− 0.92, DOR 1.11 (95% CI 0.07–15.53). In order to adjust diagnostic efficiency without a certain threshold value, the logit regression equation was calculated. The percent of concordance for UFC made 53%, MPC – 81.8%. Also there were performed comparison results of patients with and without CS: results of MPC (significant difference) and UFC (insignificant difference).
Conclusions
High prevalence of CS without specific signs was confirmed on our study (about 3%). Among tests used to screen and confirm CS without specific signs, UFC has the worst diagnostic characteristics and, therefore, should not be used. MPC has better characteristics, however, the question of threshold value has to be discussed.

DOI: 10.1530/endoabs.37.EP60

EP61

The utility of current guidelines in the assessment of adrenal incidentalomas

Emily Austin, Lisa Shepherd, Asad Rahim & Andrew Bates
Heart of England Foundation Trust, Birmingham, UK.

Adrenal incidentaloma's are a common clinical dilemma with increasing utilisation of cross-sectional imaging modalities. The aims of management include i) exclusion of possible malignancy and ii) identification of hormonally active lesions. Our unit has adopted AACE guidelines, including a screen for adrenal androgen hypersecretion. This audit aimed to review the utility of such an approach. We identified case notes of 100 consecutive adrenal incidentaloma's referred to endocrinology prior to November 2014. All were subject to radiological scrutiny by a dedicated radiologist, whilst endocrine investigations, including two 24 h urinary metanephrines, 1 mg overnight dexamethasone suppression test, renin:aldosterone ratio and DHEAS were arranged, together with electrolytes and blood pressure. Radiologically, 84% were considered to be benign adrenal adenomas on the basis of either CT density (<10 HU), CT contrast washout at 10 min (>60%) or in and out of phase MRI. 3% were myolipomas and 4% phaeochromocytomas. 8% were indeterminate and referred for further investigation or surgery. From a functional perspective, we identified four phaeochromocytomas, all of whom had imaging studies inconsistent with a benign adenoma and raised urinary metanephrines. Five had a 0900 h cortisol of >100 following 1 mg dexamethasone, none of whom had symptoms/signs consistent with cortisol excess and two of whom have already had cortisol excess excluded by further investigation. The remainder have further investigations pending. Two males had elevated DHEAS levels and both had abnormal imaging, one of which proved to be a phaeochromocytoma. There were no abnormal renin:aldosterone ratios. 89% of the cohort was hormonally inactive. On the basis of this audit, we are concerned that adrenal incidentalomas are currently over-investigated. In patients with no symptoms/signs of an underlying endocrinopathy, normal blood pressure, normokalaemia and imaging consistent with a benign adenoma, universal endocrine investigation is largely unrewarding.

DOI: 10.1530/endoabs.37.EP61

EP62

Prospective evaluation of cardiovascular risk in subclinical Cushing's syndrome

Serkan Yener[1], Yasin Cekdemir[2], Mustafa Baris[2], Mustafa Demirpence[3], Tevfik Demir[1] & Mustafa Secil[2]
[1]DEUTF, Division of Endocrinology, Izmir, Turkey; [2]DEUTF, Department of Radiology, Izmir, Turkey; [3]Tepecik EAH, Division of Endocrinology, Izmir, Turkey.

Introduction
Natural history of adrenal incidentalomas has not been totally understood. Current data from subjects with adrenal incidentalomas demonstrated an increased rate of metabolic disturbances and cardiovascular risk. It has been shown that subjects with subclinical cortisol excess were more susceptible to diabetes, hypertension, and obesity. However, there is no data regarding prospective cardiovascular risk evaluation in subjects with subclinical Cushing's syndrome.
Methods
Patients referred to Dokuz Eylul University between January 2013 and January 2014 were included. Patients with subclinical Cushing's syndrome ($n=20$), patients with non functioning adrenal adenomas ($n=30$) and subjects without adrenal adenomas ($n=25$) were enrolled. Interventions included physical examination, anthropometric measures, imaging with CT (MRI if CT was contraindicated), 1 mg DST, ACTH, UFC, urinary catecholamine levels, PAC/PRA (if indicated), hcCRP, lipid profile, HOMA index, and fibrinogen levels. Additionally all subjects underwent carotid intima media thickness (IMT) measurement and evaluation of flow mediated dilatation (FMD) of the brachial artery All laboratory tests were repeated in both groups after 12 months follow up.
Results
Baseline anthropometric parameters were comparable. Briefly, patients with subclinical Cushing's syndrome did not exhibit any deteriorations in IMT of the carotid arteries or FMD of brachial artery after 12 months follow up.
Discussion
Although subclinical Cushing's syndrome is associated with several cardio-metabolic disturbances, endothelial function does not seem to be altered in 12 months follow up. Therefore, the decision of adrenalectomy vs follow up should be conservative and short-term follow up seems feasible.

DOI: 10.1530/endoabs.37.EP62

EP63

Salivary cortisol values among nurses at Pathology and Emergency Department

Blertina Dyrmishi[1], Taulant Olldashi[1], Emirvina Kolici[2], Zamira Ylli[2] & Agron Ylli[2]
[1]Hygeia Hospital, Tirana, Albania; [2]Neo Style Clinic, Tirana, Albania.

Aim
To see the difference between salivary cortisol values and correlation with the work stress.
Methods
The salivary and serum cortisol values were analysed in two groups of nurses, six nurses in the Emergency Department and six nurses in the Pathology Department at our hospital, three females and three males for each group. The samples were taken before beginning the work and after finishing the work. The cases respected all the rules for salivary testing of cortisol and the average age of the participants was the same for both groups, 28.5 years old.
Results
Median serum cortisol values in the Emergency Department in the morning were 188.8 nmol/l (normal range 55–230) and median salivary cortisol values 3.1 μg/dl (normal range 1–11.3) and at the end of work (1600 h) the values were: serum cortisol values 130.2 nmol/l (normal range 28–140) and salivary cortisol values 1.87 μg/dl (normal range 0.2–2.7). In the Pathology Department: in the morning (0800 h) average serum cortisol values were 125 nmol/l and salivary cortisol values 2.1 μg/dl and at the end of the work (1600 h): serum cortisol values were 94.0 nmol/l and salivary cortisol values 1.22 μg/dl.
Conclusions
Since the stress of work is higher in the Emergency Department, even the results of the salivary cortisol values were higher in the nurses of the Emergency Department compared to the nurse of Pathology Department and there existed a correlation between salivary and serum values, but the study needed a bigger group of nurses to have more trustful conclusions.

DOI: 10.1530/endoabs.37.EP63

EP64

Serum brain-derived neurotrophic factor in Cushing's syndrome patients

Alicia Santos[1], Eugenia Resmini[1], Ma José Barahona[2], Iris Crespo[1], Elena Valassi, Ma Antonia Martinez[3], Ana Marin[4] & Susan M Webb[1]
[1]Endocrinology/Medicine Departments, Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBER-ER, Unidad 747), Hospital Sant Pau, IIB-Sant Pau, ISCIII and Universitat Autònoma de Barcelona, Barcelona, Spain; [2]Endocrinology Department, Hospital Universitari Mútua de Terrassa, Terrassa, Spain; [3]Escola Universitària d'Infermeria, Hospital de Sant Pau, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain; [4]Internal Medicine Department, Hospital Sant Pau, Barcelona, Spain.

Introduction
Brain-derived neurotrophic factor (BDNF) is a protein that has been linked to several cardiovascular risk factors and bone status. Stress and corticosteroid exposure can affect BDNF levels, although this has never been studied in Cushing's syndrome (CS). The aims of this study were to establish if BDNF levels were reduced in CS and to check possible associations to cardiovascular risk factors and bone status.
Methods
52 patients (18 active CS and 34 in remission) and 52 controls matched for sex and age were studied. Blood tests (including biochemistry, cortisol, and BDNF), anthropometry, complete clinical examination and a whole body DEXA were performed. Statistical analysis was performed using ANOVA with Bonferroni correction and Pearson correlations.
Results
BDNF was reduced in both active and in remission CS patients, compared to controls ($P<0.001$ and $P<0.05$). Both patient groups had higher waist ($P<0.01$ and $P<0.05$) and diastolic blood pressure ($P<0.001$ both), while CS in remission also showed higher systolic blood pressure ($P<0.01$) and triglycerides ($P<0.01$) than controls. Correlations including the whole sample showed that BDNF positively correlated with bone mineral content ($r=0.285$, $P<0.01$), meaning that reduced BDNF indicated less bone mineral content. BDNF also negatively correlated to diastolic blood pressure ($r=-0.210$, $P<0.05$).
Conclusion
BDNF is reduced in CS patients, even after cure. It may contribute to persistent comorbidities seen in CS patients, such as osteoporosis and hypertension.
Supported by FIS080302 and ERCUSYN PHP800200.
Disclosure
This work was supported by the Instituto de Salud Carlos III (grant number FIS 080302) and the Public Health Progam of the European Comission (ERCUSYN project, grant number PHP 800200).

DOI: 10.1530/endoabs.37.EP64

EP65

Urinary metanephrine levels can be spurious in the diagnosis of patients with phaeochromocytoma: preliminary results from a single centre

Oya Topaloglu[1], Husniye Baser[2], Cevdet Aydin[1], Ahmet Dirikoc[1], Reyhan Ersoy[1], Ozcan Erel[3] & Bekir Cakir[1]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Yildirim Beyazit University, Ankara, Turkey; [2]Department of Endocrinology and Metabolism, Atatürk Education and Research Hospital, Ankara, Turkey; [3]Department of Biochemistry, Faculty of Medicine, Yildirim Beyazit University, Ankara, Turkey.

Introduction
Phaeochromocytomas (PHEO) are diagnosed with classic findings and symptoms but biochemical confirmation must be made. Either urinary or plasma chatecholamines and metanephrines can be used for biochemical evaluation. Normal values rule out the diagnosis, whereas fourfold increase above the upper limit of normal confirm the diagnosis. But value of borderline or less than fourfold elevations in the diagnosis is not clear. We aimed to determine the urinary fractionated metanephrine and catecholamine levels in patients with PHEO.
Material and methods
Thirteen patients with final diagnosis of PHEO (PHEO group) and ten patients (non-PHEO group) who underwent to adrenalectomy and finally diagnosed as benign neoplasm (six adenomas, three cysts, and one hyperplasia) were evaluated retrospectively. Urinary metanephrines were evaluated by HPLC.

Results
In PHEO group urinary metanephrines were as follows: 3 (25%) had borderline elevations, 9 (75%) had normal values, however 1 (10%) had borderline elevation, 1 (10%) had sixfold elevations, and 8 (80%) had normal values in non-PHEO group. The difference was evaluated as statistically insignificant ($P=0.19$). Normetanephrine values were as follows: borderline elevation in 5 (41.7%), twofold elevation in 1 (8.3%), sixfold elevation in 1 (8.3%), and normal values in 5 (41.7%) patients in PHEO group; borderline elevations in 2 (20%), twofold elevation in 1 (10%), normal values in 7 (70%) patients in non-PHEO group. This was also statistically insignificant ($P=0.39$). There were also no significant differences in urinary adrenaline and noradrenaline levels between groups.
Conclusion
Patients with borderline-elevated urinary metanephrine levels can also have PHEO. In patients with adrenal incidentalomas who are candidate for surgery and have borderline elevated metanephrines should be evaluated carefully. In this group of patients, we advocate either routine preoperative preparation as patients possessing PHEO or further diagnostic tests in order to prevent the serious complications.

DOI: 10.1530/endoabs.37.EP65

EP66

Clinical significance of contralateral adrenal suppression during adrenal vein sampling in primary aldosteronism

Silvia Monticone[1], Fumitoshi Satoh[2], Andrea Viola[1], Eveline Fischer[3], Oliver Vonend[4], Giampaolo Bernini[5], Marcus Quinkler[6], Gilberta Giacchetti[7], Ryo Morimoto[2], Holger Willemberg[4], Mauro Maccario[1], Franco Veglio[1], Sadayoshi Ito[2], Martin Reincke[3] & Paolo Mulatero[1]
[1]University of Torino, Torino, Italy; [2]Tohoku University, Sendai, Japan; [3]Ludwig Maximilian University, Munich, Germany; [4]University of Düsseldorf, Düsseldorf, Germany; [5]University of Pisa, Pisa, Italy; [6]Charité University Medicine Berlin, Berlin, Germany; [7]Università Politecnica delle Marche, Ancona, Italy.

Objective
Adrenal vein sampling (AVS) is recognised by Endocrine Society guidelines as the only reliable mean to distinguish between aldosterone producing adenomas and bilateral adrenal hyperplasia, the two most common subtypes of primary aldosteronism (PA). However, AVS protocols are not standardised and vary between centres. The objective of the present study was to assess whether the presence or absence of contralateral adrenal (CL) suppression has an impact on the postoperative clinical and biochemical parameters in patients who underwent unilateral adrenalectomy for PA.
Design and methods
The study was retrospectively carried out in eight referral hypertension centres in Italy, Germany, and Japan. Screening and subtype differentiation were performed according to the Japan Endocrine Society and the Endocrine Society guidelines and a total of 234 AVS procedures were included in the study. CL suppression was defined as $\text{aldosterone/cortisol}_{\text{nondominantadrenalvein}}/\text{aldosterone/cortisol}_{\text{peripheralvein}} < 1$.
Results
Overall, 82% of patients displayed CL suppression at AVS, with no statistically significant differences among centres. This percentage was significantly higher in ACTH-stimulated compared with basal procedures (90% vs 77%). The CL ratio was inversely correlated with the aldosterone level at diagnosis and, among AVS parameters, with the lateralisation index ($P<0.02$ and $P<0.01$ respectively). To investigate whether the presence of CL suppression was correlated with response to adrenalectomy, we analysed the CL suppression status with regard to the patient's clinical and biochemical postoperative parameters. No differences were observed between the two groups for the main clinical and biochemical parameters (systolic and diastolic blood pressures, aldosterone, PRA, PRC, K^+, number of drugs, reduction of blood pressure levels, and the number of classes of drugs assumed), but patients with CL suppression underwent a significantly larger reduction in aldosterone levels after adrenalectomy.
Conclusions
For patients with lateralisation indices of >4, CL suppression should not be required to refer patients to adrenalectomy because it is not associated with a larger blood pressure reduction and might exclude patients from curative surgery.

DOI: 10.1530/endoabs.37.EP66

EP67

Glucocorticoid receptor polymorphisms not affect the therapy efficiency in adult, Hungarian patients with 21-hydroxylase deficiency

Koncz Klára[1,2], Farkas Abigél[1], Doleaschall Marton[3], Szücs Nikolett[1], Tóth Miklós[1], Igaz Péter[1], Rácz Károly[1] & Patócs Attila[1,2]
[1]2nd Department of Medicine, Semmelweis University, Budapest, Hungary; [2]'Lendület' Hereditary Endocrine Tumors Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest, Hungary; [3]Molecular Medicine Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest, Hungary.

Background
Congenital adrenal hyperplasia (CAH) is an autosomal recessive inherited disorder caused by 21-hydroxylase deficiency in 95% of all cases. Two main clinical subtypes: the classical (manifested after birth, or in early newborn period) and the late onset (LO) phenotype (manifested commonly during puberty). The lifelong glucocorticoid (GC) supplementation is essential in therapy of these patients. Response to GC therapy is individual and partly genetically determined.
Objective
Our aim was to study the effect of three well-known polymorphisms (SNPs; BclI, N363S, A3669G) of the GR on therapy, clinical, and laboratory parameters in gene in adult Hungarian patients with 21-hydroxylase deficiency.
Patients and methods
The diagnosis of 21-hydroxylase deficiency was based on clinical, laboratory, and molecular genetic tests including the identification of the most common *CYP21A2* gene mutations and determination of the allelic copy number (CN) of the *CYP21A2* gene. In 93 patients (54 classical and 39 late-onset, age: 28.8 ± 13.7 years) with 21-hyídroxylase deficiency the BclI and N363S polymorphisms were measured using allele-specific PCR, the A3669G polymorphism and the CN variations were detected by real-time qPCR. Allele frequencies of GR polymorphisms were compared to a Hungarian, control population ($n=160$). Association between GR SNPs and clinical, hormone laboratory, and GC supplementation dosage was studied.
Results
Allelic frequency of the GR polymorphisms did not differ from those observed in control population and did not associate with clinical, laboratory parameters or dosage of the GC supplementation. The CN of the *CYP21A2* in both groups of patients a significantly negatively correlated with GC therapy ($P=0.03$).
Conclusion
The GR polymorphisms associated sensitivity against glucocorticoids is not a major factor in determination of the dose of glucocorticoid supplementation. The *CYP21A2* CN measurement is a rapid, cheap and sensitive method for prediction the GC need in patients with 21-hydroxylase deficiency.

DOI: 10.1530/endoabs.37.EP67

EP68

The antidiabetic drug metformin affects H295R cells proliferation

Roberta Armignacco, Giada Poli, Giulia Cantini, Letizia Canu, Michaela Luconi & Massimo Mannelli
Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy.

Adrenocortical carcinoma (ACC) is a rare, heterogeneous malignancy with a poor prognosis, particularly when metastatic at diagnosis. To date, radical surgery, possibly associated to mitotane adjuvant therapy, is the only available treatment. However, the mean 5-year survival rate drops under 10% in metastatic ACC and chemo-resistance often develops. Thus, more specific and effective drugs for ACC treatment are urgently required. The antidiabetic drug metformin, used in type 2 diabetes treatment, has been associated with decreased cancer incidence and mortality in several human cancers, suggesting us the possibility to test its potential efficacy on ACC too. Our study wants to evaluate the potential anti-cancer effects of metformin *in vitro* on H295R adrenocortical tumour cell line. Treating cells with increasing doses of metformin (0.5–250 mM) affects cell viability and proliferation in a dose- and time-dependent manner, as we observed by MTS and cell count assay (IC_{50} after 7days: 23.8 ± 0.9 and 10.1 ± 0.3 mM respectively). This inhibitory effect was also confirmed by [^{3}H]thymidine incorporation assay. Moreover, combining metformin and mitotane leads to a synergistic effect which reduces cell viability more than metformin alone (IC_{50} after 7days: 16.7 ± 1.1 mM). To further investigate the molecular mechanisms by which metformin inhibits cell growth, we performed western blot analysis after 6 and 24 h treatment with different doses of metformin (20, 50, and 100 mM), and

we analysed some of the signalling pathways related to cell proliferation and survival. We observed a dose-dependent decrease of ERK1/2 phosphorylation and an increase of AMPK activation, associated with a decreased mTOR phosphorylation. In conclusion, our data suggest that metformin interferes *in vitro* with H295R proliferation, showing a synergistic effect when combined with mitotane. Further studies have to be performed *in vivo* by using animal models to prove the potential anti-cancer effect of metformin in adrenocortical carcinoma.

Disclosure
ENS@T CANCER – FP7/2007-2013 (grant number 259735). MIUR-FIRB 2010 (grant number RBAP1153LS).
DOI: 10.1530/endoabs.37.EP68

EP69

Prevalence and natural history of adrenal incidentalomas: a prospective cohort study

Panagiotis Anagnostis, Athanasios Siolos, Chrisanthi Zouli, Fotini Adamidou, Zoe Efstathiadou, Athanasios Panagiotou, Gesthimani Mintziori & Marina Kita
Department of Endocrinology, Hippokration Hospital of Thessaloniki, Thessaloniki, Greece.

Introduction
Adrenal incidentalomas (AIs) are frequently detected due to the increasing use of abdominal imaging for diagnostic purposes. However, few prospective studies exist with respect to their natural history, regarding their size and clinical course. The aim of this study was to report the prevalence and natural history of AIs.
Methods/design
Interim analysis of a prospective cohort study. The following tests were performed: serum cortisol nocturnal rhythm, 24 h-urinary free cortisol, low-dose dexamethasone suppression test, aldosterone to plasma-renin-activity ratio and 24 h-urinary total metanephrines and catecholamines. In cases of positive results, confirmatory tests were performed. Radiological assessment was repeated at 6–12 months and yearly thereafter.
Results
Sixty-four patients (19 (30%) males, mean age 59.7 ± 12.1 years) were included. Follow-up data were available for 57 AIs (median time: 36 months, range 4–84). Median size was 2.5 mm (range 0.5–6.5) (unilateral adenoma in 50 (78%)). The final diagnosis was: 56 non-functioning adenomas (87.5%), 5 (7.8%) subclinical Cushing's syndrome (SCS), 1 (1.6%) phaeochromocytoma, 1 (1.6%) aldosteronoma, and two adrenocortical carcinomas (3.2%), of which one had also SCS. Mass enlargement (9 mm) was observed in one patient (2.8%), while a decrease (7–27 mm) in 3 (8.5%). No hormonal evolution was noticed. Regarding glucose metabolism, 12, 16.7, and 20% of the patients presented deterioration in glucose metabolism at the first, second, and third year of follow-up respectively. The respective percentages for dyslipidaemia were 26, 43, and 44% and for hypertension or blood pressure worsening were 38, 44, and 48%. After excluding those with SCS, these percentages did not alter significantly. New cardiovascular events or fractures were recorded in 7.8% of the patients.
Conclusions
The vast majority of AIs involved benign, non-secretory masses. Mass enlargement was rare. More than one-third of patients developed hypertension or their lipid profile worsened, while one fifth showed deterioration in glucose metabolism, irrespectively of the presence of SCS.

DOI: 10.1530/endoabs.37.EP69

EP70

Prevalence of hypercortisolism in type 2 diabetes patients: a meta-analysis

Charlotte Steffensen[1], Alberto Pereira[2], Olaf M Dekkers[2,3] & Jens Otto Jørgensen[1]
[1]Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark; [2]Department of Endocrinology/Epidemiology, Leiden, The Netherlands; [3]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark.

Background
Type 2 diabetes (T2D) and hypercortisolism associated with Cushing's syndrome (CS) share clinical characteristics such as hypertension, dyslipidaemia, hyperglycaemia, and obesity. Several studies have recorded a relatively high prevalence of hypercortisolism in T2D, which may have therapeutic implications. The aim of this systematic review and meta-analysis was to assess the prevalence of hypercortisolism in T2D patients.
Methods
Original articles assessing the prevalence of endogenous CS in T2D were eligible. A search was performed in SCOPUS, MEDLINE, and EMBASE. Data were pooled in a random effects logistic model.
Results
Fourteen articles were included, with a total of 2827 T2D patients. The reported prevalence of hypercortisolism in T2D ranged between 0 and 12.1%. The pooled prevalence of hypercortisolism in T2D was 3.6% (95% CI 3.0–4.4). The prevalence did not differ between studies of unselected patients and patients selected on the basis of complications such as obesity or poor glycaemic control ($P = 0.41$). Imaging in patients with hypercortisolism ($n = 102$) revealed adrenal tumour(s) and pituitary tumours in 14 and 52% respectively.
Conclusion
Hypercortisolism is a reproducible and relatively frequent finding in T2D. This observation merits continued interest.

DOI: 10.1530/endoabs.37.EP70

EP71

Fludrocortisone therapy in patients with primary adrenal insufficiency: relationships with different hydrocortisone doses

Bertil Ekman[1], Marcus Quinkler[2], Beverly A Jones[3], Claudio Marelli[4], Robert Murray[5], Pierre Zelissen[6] & Jeanette Wahlberg[1]
[1]Department of Medical and Health Sciences, Linköping University, Linköping, Sweden; [2]Endokrinologie in Charlottenburg, Berlin, Germany; [3]Shire PLC, Chesterbrook, Pennsylvania, USA; [4]Shire International GmbH, Zug, Switzerland; [5]Leeds Teaching Hospitals NHS Trust, Leeds, UK; [6]University Medical Center Utrecht, Utrecht, The Netherlands.

Introduction
During recent years many authors have advocated lower hydrocortisone doses in patients with primary adrenal insufficiency (PAI) mainly due to worries for non-physiological effects like increased cardiovascular risk and bone resorption, but very little attention has been drawn to fludrocortisone dosing. Our main hypothesis was that that the higher hydrocortisone dose, the lower the fludrocortisone dose and *vice versa*.
Design
The European Adrenal Insufficiency Registry (EU-AIR) sponsored by Shire with 20 centers in Germany, The Netherlands, Sweden and the UK started enrolling patients with AI in August 2012. At enrolment, comprehensive demographic and baseline data, etiology of PAI, details of glucocorticoid replacement therapy and safety data (intercurrent illnesses, adrenal crisis) are collected electronically. This report compares baseline data of PAI (including classic adrenal hyperplasia (CAH)) treated with hydrocortisone/cortisone acetate or the new modified release hydrocortisone tablet (Plenadren) given in lower doses ≤ 20 mg or doses > 20 mg with regards to the dose of fludrocortisone.
Results
As of 5th November 2014, 345 patients with PAI, 50.1 ± 15.7 years., 221 (64.1%) F, BMI < 25 44.1%, 25–< 30 30.4% and ≥ 30 18% (missing BMI data 7.5%), were registered in EU-AIR. The distribution of hydrocortisone-equivalent doses were: $n = 179$ received ≤ 20mg, while $n = 166$ received > 20 mg (of those $n = 27$ received > 30 mg). The median fludrocortisone dose for all patients was 100 μg (range 0–300). No clear differences were found between gender, but a tendency to higher doses of fludrocortisone in males, if treated with hydrocortisone < 20 mg, was found. On the other hand, increasing doses with fludrocortisone were slightly associated with higher BMI and with hydrocortisone doses > 30 mg.
Conclusions
Our data shows that the fludrocortisone dose differs widely between patients. We could not demonstrate a general effect that higher hydrocortisone doses compensating the mineralocorticoid effect with correspondingly lower doses of fludrocortisone in PAI.

Disclosure
This work was sponsored by Shire.
DOI: 10.1530/endoabs.37.EP71

EP72

Prevalence of Cushing's syndrome at overweight and obese patients

Mehtap Navdar Basaran[1], Berçem Ayçiçek Doğan[1], Eda Demir Önal[1], Ersen Karakılıç[1], Dilek Berker[1] & Serdar Güler[1,2]
[1]Numune Education and Training Hospital Endocrinology Department, Ankara, Turkey; [2]Hitit University Medical Faculty Endocrinology Department, Çorum, Turkey.

Background
In the presence of specific symptoms and signs, Cushing's syndrome (CS) may be easily recognised. On the other hand, in overweight and obese patients without typical features of CS, diagnosis may be omitted. Our aim was to evaluate the prevalence of CS among overweight and obese patients.
Methods
We enrolled 264 overweight and obese patients who has not overt CS clinical features between January 2012 and December 2014 at Ankara Numune Education and Training Hospital. All patients were screened via overnight 1 mg dexamethasone suppression test (DST). Patients who had positive screening test has undergone other diagnostic tests.
Results
In eleven patients cortisol levels has not been supressed under 1.8 μg/dl after overnight 1 mg DST. Overnight 2 mg DST cortisol levels were supressed under 1.8 μg/dl in these four patients. The remaining seven patients (five women, two men) CS were confirmed with a standard 2-day, 2-mg DST, and high late-night salivary cortisol levels (2.6%). While six of them were ACTH-dependent CS, only one were adrenal CS. Mean BMI of CS patients was 38.3 kg/m^2, the remainings mean BMI was 38.8 kg/m^2. There was four predibaetes and two diabetes mellitus patients in CS group. Four of CS patients were hypertensive.
Conclusion
We found prevalence of CS 2.6% in overweight and obese patients whether or not accompanying overt DM or HT. Overnight 2 mg DST results yielded more specific results than 1 mg DST. Based on these results we consider screening CS with 2 mg DST in this population may be reasonable.

DOI: 10.1530/endoabs.37.EP72

EP73

The clinical course of patients with adrenal incidentaloma: is it time to reconsider the current recommendations?

Darko Kastelan[1,2], Ivana Kraljevic[2], Tina Dusek[1,2], Nikola Knezevic[2], Mirsala Solak[2], Bojana Gardijan[2], Marko Kralik[2], Tamara Poljicanin[3], Tanja Skoric Polovina[2] & Zaljko Kastelan[1,2]
[1]Zagreb University School of Medicine, Zagreb, Croatia; [2]University Hospital Center Zagreb, Zagreb, Croatia; [3]Croatian National Institute of Public Health, Zagreb, Croatia.

Context
The current guidelines for the management of adrenal incidentaloma advise hormonal and radiological follow-up of the patients for 2–5 years after the initial diagnosis. However, a vast majority of adrenal incidentaloma are non-functional, benign cortical adenomas that require no treatment, so the routine application of the current strategies often results in a number of unnecessary biochemical and radiological investigations.
Objective
The aim of this study was to analyse the clinical course of patients with adrenal incidentaloma and to provide a critical review of the current management strategy of the disease. Design and setting: This was a retrospective study performed in the Croatian Referral Center for adrenal gland disorders. Patients: The study included 319 consecutive patients with adrenal incidentaloma 174 of which were followed for at least 24 months.
Results
A vast majority of patients were diagnosed with benign adrenal masses whereas in about 5% of them adrenal tumour corresponded to adrenal carcinoma or metastasis. Tumour density was found to be superior to tumour size in distinguishing benign adrenal masses from malignant tumors and pheochromocytomas. During the follow-up no patient demonstrated a clinically significant increase in tumour size. In addition, no changes, either in metanephrines and normetanephrines or in the activity of renin-aldosterone axis, were observed during the follow-up. Six patients developed SCS.
Conclusion
The study indicates that the risk of an adrenal mass initially diagnosed as benign and non-functional to become malignant or hormonally active is rather low. Therefore, the clinical management of those patients should be tailored on an individual basis in order to avoid unnecessary procedures.

DOI: 10.1530/endoabs.37.EP73

EP74

An audit of the investigation and follow up of adrenal incidentalomas

Fred McElwaine, Peter Ellis, David McCance, Patrick Bell, Steven Hunter, Hamish Courtney & Karen Mullan
Royal Victoria Hospital, Belfast, UK.

An adrenal incidentaloma is defined as an adrenal mass >1 cm diameter, discovered serendipitously on radiological imaging done for another reason. They are important because a percentage will turn out to be malignant or secrete excess hormones. The aim of the current study was to ascertain if these lesions were being investigated and followed appropriately compared to American Association of Clinical Endocrinologists guidelines. All imaging reports for the calendar year 2010 were searched for the terms 'adrenal' and 'adenoma' and then checked manually. Imaging done for staging of cancer or for investigation of possible adrenal disease was excluded. 95 patients were identified. Clinical information was obtained form the Northern Ireland Electronic Care Record and clinical notes. Incidentalomas were commoner in older patients, 49 of the patients were over 70 years of age. 64 patients had no follow up imaging performed, including two patients with lesions greater than 4 cm in diameter. Three patients were under the care of endocrinology or endocrine surgery. 19 patients were referred to endocrinology. 25 patients were screened for hypercortisolaemia, 25 were screened for phaeochromocytoma, 70 patients underwent no screening for hormonal excess. 35 patients had a history of hypertension but only nine were screened for primary hyperaldosteronism. All patients referred to endocrinology or endocrine surgery were investigated according to guidelines. Only three patients not referred to endocrinology underwent appropriate investigations with screening for hypercortisolaemia or phaeochromocytoma. In summary, the majority of adrenal incidentalomas are not followed up appropriately. To address this radiology will, in future, advise endocrine referral for patients with incidentally detected adrenal lesions >1 cm in diameter.

DOI: 10.1530/endoabs.37.EP74

EP75

Biochemical control and clinical improvement is induced by long-term pasireotide administration in the majority of patients with Cushing's disease persistent after pituitary surgery

Erika Messina, Adriana Albani, Francesco Ferrau, Francesco Trimarchi & Salvatore Cannavo
Department of Clinical and Experimental Medicine – Endocrinology, University of Messina, Messina, ME, Sicily, Italy.

Pasireotide (SOM230) is a multireceptor ligand somatostatin analogue with high binding affinity to somatostatin receptor subtype 5, which is predominantly expressed in ACTH-secreting pituitary adenomas. It is indicated for the treatment of adult patients with Cushing's disease (CD) for whom pituitary surgery is not an option or has not been curative. Our study evaluated the effects of pasireotide, administered for 12 months at a dose of 600–900 μg/daily, in five CD patients with persistent/recurrent disease after pituitary surgery. 24-h urinary free cortisol (UFC) levels, weight, BMI, waist circumference, blood pressure and glucose and lipid metabolism parameters were evaluated in all patients. After 6 months of therapy 4/5 patients (80%) had normal UFC levels, confirmed at 12 months. UFC normalization was associated with a slight improvement in anthropometric values and amelioration of lipid profile. In the remaining 20% of patients (1/5), normalization of UFC levels after 1 month of therapy was followed by escape from response. No patient experienced adrenal insufficiency. Hyperglycaemia due to pasireotide therapy occurred in two patients with normal glucose metabolism prior to treatment. These findings suggest that Pasireotide is an

effective treatment for most of the patients with persistent/recurrent CD after surgery.

DOI: 10.1530/endoabs.37.EP75

EP76

Ectopic thyroid tissue in the adrenal gland: report of a case

Emre Bozkirli[1], Okan Bakiner[1], Sedat Belli[2], Emrah Kocer[3], Serife Ulusan[4] & Mehmet Reyhan[5]
[1]Endocrinology Department, Faculty of Medicine, Baskent University, Adana, Turkey; [2]General Surgery Department, Faculty of Medicine, Baskent University, Adana, Turkey; [3]Pathology Department, Faculty of Medicine, Baskent University, Adana, Turkey; [4]Radiology Department, Faculty of Medicine, Baskent University, Adana, Turkey; [5]Nuclear Medicine Department, Faculty of Medicine, Baskent University, Adana, Turkey.

Background
Ectopic thyroid tissue (ETT) can be explained as the localisation of thyroid parenchyma outside the orthotopic position of the thyroid gland. It can be more easily found in the tongue, neck, mediastinum, great vessels, heart and anywhere along Wölfler area, but presentation in the adrenal glands is absolutely very rare.
Case
A 39-year-old woman was referred to our Endocrinology outpatient clinic with an incidental adrenal mass which was seen in abdomen CT performed because of a nonspecific abdominal pain. Her abdomen CT revealed a 13×18 mm non-adenoma solid mass in the right adrenal gland which showed 43 Hounsfield units (HU) in precontrast series, 71 HU in portal phase and 67 HU in late phase. Endocrinologic evaluation showed that it was a non-functional tumour. Her PET CT scan revealed a hypermetabolic nodular lesion in the right adrenal gland and physiological FDG uptake in bilateral adnexal regions. The patient underwent surgery and histological examination showed thyroid tissue in the adrenal gland seen as large islets. No sign of atypia was observed. Immunohistochemical studies were negative for CK-19, HBME-1 and GAL-3. Patient's thyroglobulin level was within normal ranges as 23.80 ng/ml (1.60–55). She had a subtotal thyroidectomy history and her current neck USG revealed several benign appearing thyroid nodules with the largest as 12×9 mm in diameter. A thyroid fine needle aspiration biopsy was performed and found as benign.
Conclusion
To date, intraadrenal ETT has been reported in ten cases in the literature. Only one of them was solid like our case, and the remaining were cystic lesions. Clinicians and pathologists must be careful during distinguishing it from metastatic thyroid cancer. For our case we planned a complementary thyroidectomy to exclude a metastatic thyroid cancer. However her PET CT scan results, thyroglobulin level, benign appearance of thyroid nodules, benign biopsy result and absence of any other solid organ metastasis may propose an existence of ETT in the adrenal gland.

DOI: 10.1530/endoabs.37.EP76

EP77

Prevalence of neoplasms in patients with primary aldosteronism

Katharina Lang[1,2], Katrin Weber[1], Marcus Quinkler[3], Anna Dietz[4], Henri Wallaschofski[5], Anke Hannemann[5], Oliver Vonend[6], Holger Willenberg[7], Martin Reincke[4], Bruno Allolio[1] & Stefanie Hahner[1]
[1]Department of Internal Medicine I, Endocrinology and Diabetology and Comprehensive Heart Failure Center, Wuerzburg, Germany; [2]Centre for Endocrinology, Diabetes and Metabolism, University of Birmingham, Birmingham, UK; [3]Clinical Endocrinology, Charité Campus Mitte, Charité University Medicine, Berlin, Germany; [4]Medizinische Klinik und Poliklinik IV, University Hospital Munich, Munich, Germany; [5]Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Germany; [6]Department of Nephrology, Medical Faculty, Heinrich- Heine Universitaet Duesseldorf, Duesseldorf, Germany; [7]Division for Specific Endorinology, Medical Faculty, University Duesseldorf, Germany, Duesseldorf, Germany.

Context
Primary aldosteronism (PA) is the most common cause of secondary hypertension. Aldosterone excess can cause oxidative stress and respectively DNA damage *in vitro* and *in vivo* and increased levels of oxidative stress have been demonstrated in PA patients. Single case reports describe a coincidence of PA with renal cell carcinoma (RCC) and other tumours. However, so far no data on the prevalence of benign and malignant neoplasms in patients with PA exists.
Patients and methods
In the multicentre MEPHISTO study the prevalence of benign and malignant tumours was investigated in 338 patients with confirmed PA both retro- and prospectively. The SHIP cohort served as a matched control group for subjects with primary hypertension.
Results
Of the 338 patients, 120 (35.5%) had been diagnosed with a tumour at any time, 31 had more than one tumour diagnosis. Malignancy at any life stage was reported in 9.5% of PA patients and in 6.0% of hypertensive controls ($P=0.08$). Interestingly, PA patients with malignancies in history had significantly higher baseline aldosterone levels at initial diagnosis of PA ($P=0.009$) and a positive correlation between aldosterone levels and prevalence of malignancies was observed ($P=0.02$). In total, 159 neoplasms were identified in the PA patients, which were benign in 62% and malignant in 24% of cases. RCC was diagnosed in five patients (13% of all malignancies) and 80% of RCC patients had been diagnosed with renal cysts prior to tumour diagnosis. The relation between tumour formation and aldosterone levels was most abundant in PA patients with RCC.
Conclusion
In this cohort of PA patients a trend towards an increased lifetime prevalence for malignancies was observed which was particularly obvious for RCC and correlated significantly with baseline aldosterone levels.
Disclosure
Else-Kroener-Fresenius

DOI: 10.1530/endoabs.37.EP77

EP78

Outcomes of short synacthen test in a university teaching hospital: are baseline and time 30 min sufficient?

Mohamed Ahmed[1], Gunness A[1], Rakovac-Tisdall A[2], Cullen E[1], Barnwell N[1], Neary C[1], Boran G[2], Gibney J[1] & Sherlock M[1]
[1]Department of Endocrinology, The Adelaide and Meath Hospital incorporating the National Children's Hospital, Tallaght, Dublin, Ireland; [2]Department of Chemical Pathology, The Adelaide and Meath Hospital incorporating the National Children's Hospital, Tallaght, Dublin, Ireland.

Introduction
Short synacthen test (SST) has become the standard method of assessing the hypothalamic–pituitary–adrenal (HPA) axis. However, there are still variances in practice with regards to performing and interpreting this test in particular the need for measuring cortisol level at both time 30 and 60 min.
Methods
A retrospective review of 500 consecutive SST performed at a University teaching Hospital in Dublin between 2005 and 2012. Serum cortisol was measured at time 0, 30, and 60 min following synacthen. A cortisol level of >500 nmol/l was considered adequate to out rule adrenal insufficiency.
Results
Out of 500 patients, 297 (59.4%) were females, and the average age was 57.4±19.3 years. 215 (43%) of subjects had at least one random cortisol level checked in the preceding 6 months prior to the synacthen test date, and the mean random cortisol for those who passed the test was 367.6±195.7 nmol/l compared to 133.5±81.8 in those who failed it, $P<0.01$. 225 (45%) of patients had at least one low serum sodium (<135 nmol/l) during the 6 months prior to test. Hyponatraemia was more prevalent in those who failed the test compared to those with adequate cortisol response (58% vs 43%, $P<0.05$).
438 (87.6%) patients passed their SST at both time 30 and 60 min and 53 (10.6%) failed it. In nine cases only (1.8%), the peak value of >500 nmol/l was achieved at time 60 but not at time 30 min.
Conclusion
Our data shows that patients with low random cortisol and hyponatraemia in the 6 months prior to the SST are likely to fail it. Measuring the baseline and time 30 min cortisol will lead to the correct diagnosis in over 98% of cases. Checking cortisol level at time 60 is of little added value in the majority of cases.

DOI: 10.1530/endoabs.37.EP78

EP79

Functional muscle capacity and daily physical activity deficits in patients with endogenous Cushing's syndrome

A Assimakopoulou[1], Z Louvaris[2], M Balomenaki[1], N Chynkiamis[2], M Tzanela[1], I Vogiatzis[2] & S Tsagarakis[1]
[1]Department of Endocrinology, Diabetes and Metabolism 'Evangelismos Hospital', Athens, Greece; [2]Department of Physical Education and Sports Science, National and Kapodistrian University, Athens, Greece.

Cushing's syndrome (CS) is a disease entity that through hypercortisolism affects all body's tissues leading to increased morbidity, decreased quality of life and mortality. Muscles are among the tissues primarily affected. However, data on the impact of endogenous hypercortisolism on functional muscle capacity and daily physical activity levels are scarce. We studied 23 subjects with endogenous CS (mean age: 40.73 ± 2.17 years) and 22 healthy aged and sex matched controls. Assessment of the degree of hypercortisolism was based on cortisol day-curve, midnight cortisol and 24 h urine cortisol levels (UFC). Body composition was measured by bioelectrical impedance method (BIA). Functional capacity was assessed by the 6-min walking distance test (6MWT) and by quadriceps muscle strength and endurance during maximal isometric voluntary contraction test (QMVC). Respiratory muscles strength was assessed during maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) manoeuvres. Daily physical activity in terms of number of steps (steps/day) and body movement acceleration (VMU/min) was recorded by a triaxial accelerometer (Actigraph GT3X) during 7 consecutive days. The fat mass was greater in CS patients compared to controls ($P=0.005$). No differences were found between the two groups in the parameters of MIP ($P=0.79$) and MEP ($P=0.66$). Muscle force and endurance were significantly compromised in patients with CS ($P=0.04$). Six minute walking distance covered was lower in CS group ($P<0.001$). In addition, 6MWT was well correlated with time lapsed since diagnosis ($P=0.02$). Daily physical activity levels were lower in CS group compared to controls (steps/day, $P=0.0001$, and VMU/min, $P=0.0001$). Finally, there was a strong negative correlation between daily physical activity in terms of body movement acceleration (VMU/min) and biochemical indices of hypercortisolism. In conclusion, endogenous hypercortisolism has a profound negative influence on various parameters related to functional capacity and daily physical activity and these measurements may be a useful tool.

DOI: 10.1530/endoabs.37.EP79

EP80

Metabolic abnormalities in patients with nonfunctional adrenal incidentaloma: random or causal?

Alina Daniela Belceanu[1], Ioana Armasu[1], Oana Cirdei[1], Felicia Crumpei[2], Cristina Preda[1], Letitia Leustean[1], Didona Ungureanu[3], Voichita Mogos[1] & Carmen Vulpoi[1]
[1]Endocrinology Department, University of Medicine and Pharmacy Gr. T. Popa, Iasi, Romania; [2]Radiology Department, University of Medicine and Pharmacy Gr. T. Popa, Iasi, Romania; [3]Laboratory Department, University of Medicine and Pharmacy Gr. T. Popa, Iasi, Romania.

Introduction
With a prevalence of 0.5–2% in computed tomography series, incidentally diagnosed nonfunctional adrenal tumours (NAI) become more and more common in clinical practice. It is not clear if the higher frequency of NAI in patients with metabolic syndrome is causal or random.
Patients and methods
We retrospectively analysed patients diagnosed with adrenal tumors on computed tomography in 1 year interval (January–December 2014). Including criteria was an incidentally discovery. Excluding criteria were known malignancies and signs or symptoms of hormone excess which could determine the imagistic investigation, as well as subclinical disease, with adrenal axis modifications.
Results
Study group consisted in 48 patients (40 females, eight males), aged between 31 and 80 years (mean age 59 ± 10.7). Mean BMI was 29.6 ± 5.9 kg/m^2: 12 patients with normal weight, three overweight and 33 obese. Arterial hypertension was diagnosed in 43 patients (89.58%), diabetes or impaired glucose tolerance in 25 patients (52%) and hypercholesterolemia in 45 patients (93.75%). A significant positive correlation between BMI, glucose ($r=0.69$, $P<0.05$), total cholesterol ($r=0.74$) and systolic blood pressure ($r=0.98$) values was recorded. Cortisol remained within normal limits, but a slight positive correlation with cholesterol ($r=0.38$), systolic blood pressure ($r=0.2$), glucose ($r=0.25$) and BMI ($r=0.35$) was observed.
Conclusions
It is still a matter of debate whether NAI increases the risk of metabolic syndrome, having some degree of autonomous adrenal function, with subtle modifications before measurable changes of adrenal axis. Although the retrospective nature of our data did not allow us to draw any conclusions about the cause of increased prevalence of metabolic abnormalities, we suggest that some degree of adrenal autonomy – not recognised by current methods – is responsible for increased hormonal secretion and increased metabolic risk.

DOI: 10.1530/endoabs.37.EP80

EP81

Acute adrenal insufficiency as a first sign of metastatic pulmonary carcinoma

Adina Manolachie[1], Constantin Volovat[2], Cristina Grigorescu[3], Gina Eosefina Botnariu[4], Bogdan Gafton[5], Ioana Armasu[1], Letitia Leustean[1] & Carmen Vulpoi[1]
[1]Department of Endocrinology, University of Medicine and Pharmacy 'GR. T. Popa', Iasi, Romania; [2]Departament of Medical Oncology, Iasi, Romania; [3]Department of Thoracic Surgery, University of Medicine and Pharmacy 'GR. T. Popa', Iasi, Romania; [4]Department of Diabetes, Nutritional and Metabolic Diseases, University of Medicine and Pharmacy 'GR. T. Popa', Iasi, Romania; [5]Regional Institute of Oncology, Iasi, Romania.

Introduction
Adrenal glands are common sites for secondary lesions derived from malignant tumours (lymphoma, melanoma, renal, breast, colon, and bronchopulmonary cancer). Patients with adrenal secondary lesions are typically asymptomatic but 1% may present with adrenal insufficiency as a first manifestation. We report the cases of two males with lung adenocarcinoma, first presented with acute adrenal insufficiency.
Cases presentation
Case 1: LC, 65 years old, was hospitalised for acute asthenia, anorexia, severe digestive disorder, weight loss, and hypotension, associated with hypokalaemia. Adrenal insufficiency was confirmed by increased ACTH (344 pg/ml) and low-normal cortisol (6.38 μg/dl). Steroid substitution was started with amelioration of the general status. Abdominal imagery (ultrasonography and CT) revealed enlarged adrenals and a probable secondary hepatic lesion. Liver biopsy suggested a pulmonary adenocarcinoma metastasis, for which chemotherapy was started, with favorable evolution.
Case 2: BV, 57 years old, heavy smoker and drinker, decompensated, after an intervention for Dupuytren retraction, with a primary adrenal insufficiency confirmed by the biological data. Steroid substitution was started with a good initial evolution but after 3 months he stopped the treatment and was hospitalized with adrenal crisis (cortisol <1 μg/dl). Intensive treatment was efficient but the persistence of anorexia, asthenia, and inflammatory syndrome suggested a severe underlying cause. Pulmonary radiography showed a right apical lung nodule confirmed by thoraco-abdominal CT, which also revealed bilateral adrenal invasion. Pulmonary biopsy confirmed poorly differentiated adenocarcinoma and chemotherapy schema was proposed.
Conclusions
The frequency of adrenal metastasis of primary lung cancer increases with disease progression, from 10 to 40%. However, clinical manifestations of adrenal insufficiency are significantly less frequent, probably because a destruction of more than 90% of adrenal cortex is needed for clinical symptoms. Adrenal crisis was, in our two cases, the first symptom of advanced pulmonary cancer, leading to its diagnostic and therapeutic solutions.

DOI: 10.1530/endoabs.37.EP81

EP82

Marked hypercholesterolaemia caused by mitotane adjuvant chemotherapy for adrenocortical carcinoma

Banu Sarer Yurekli, Nilufer Ozdemir Kutbay, Ilker Altun & Gokhan Ozgen
Endocrinology Department, Ege University Faculty of Medicine, Izmir, Turkey.

Aim
Mitotane (o,p′-DDD) has been used to treat adrenocortical carcinoma (ACC) for several decades. Mitotane is often given in adjuvant setting after surgical resection of ACC and treatment usually lasts 2–3 years to reduce ACC recurrence. The use of mitotane is associated with multiple adverse effects. We herein report a case of marked hypercholesterolemia in a man receiving mitotane as adjuvant chemotherapy for ACC.
Case
A 64-year-old man was admitted to our Endocrinology Department with the laboratory findings of adrenal insufficiency. Mitotane was started as adjuvant chemotherapy for ACC by the Oncology department. With the usage of 4 g mitotane for 25 days, laboratory results were as follows: ACTH: 298 pg/ml, cortisol: 5.7 µg/dl, DHEAS: 7.3 µg/dl. Hydrocortisone was started as 30 mg/day. As Potassium levels were normal with the hydrocortisone treatment, fludrocoritsone was not added to the treatment. Interestingly, the patient developed marked hyper-LDL cholesterolaemia at a level of 236 mg/dl following introduction of mitotane. Before the mitotane treatment, LDL level of the patient was 139 mg/dl. After mitotane treatment, total cholesterol was 370 mg/dl, triglyceride was 160 mg/dl, HDL was 94 mg/dl. TSH level of the patient was 1.7 µIU/ml. There was no findings of hypogonadism. There was no medical history of primary familial and secondary hyperlipidaemia. Low dose atorvastatin was started for hyperlipidaemia.
Discussion
In the literature, 21 Cushing's syndrome patients treated with mitotane exhibited increased cholesterol level (primarily LDL cholesterol) with an average of 68% increase. Mitotane may increase cholesterol by inhibiting the formation of the oxysterol. It may decrease cholesterol catabolism by inhibiting the production of cholesterol oxidase. Mitotane may be able to stimulate the activity of HMG-CoAreductase strongly enough to significantly increase LDL-cholesterol synthesis.
Conclusion
We recommend careful monitoring of serum cholesterol level following the introduction of mitotane chemotherapy.

DOI: 10.1530/endoabs.37.EP82

EP83

Fasting during Ramadan in patients with adrenal insufficiency

Melika Chihaoui, Wafa Grira, Fatma Chaker, Meriem Yazidi & Hedia Slimane
University Hospital La Rabta, Tunis, Tunisia.

Long fasting in patients with adrenal insufficiency could cause hypotension, dehydration or hypoglycaemia. No studies evaluated these risks and there is no recommendations about fasting for these patients. The aim of our study was to evaluate the potential risks of fasting during the month of Ramadan in patients with adrenal insufficiency.
Subjects and methods
It is a cross sectional study that concerned 125 subjects (97 women and 28 men, mean age = 47.8 years) followed up and treated for adrenal insufficiency (primary in 34 cases and secondary in 91 cases). These patients were questioned about fasting during the last month of Ramadan; changes in the modalities of the treatment, eventual complications, number of fasted days, and were evaluated about their disease knowledge. The mean duration of daily fast during Ramadan 2014 in Tunis was about 14 h.
Results
Fasting was allowed by the physician in 11 cases (8.8%). 59 patients tried to fast: 36 patients (28.8%) could complete the fast of the whole month and 23 patients (18.4%) stopped fasting for fatigue in 20 cases, hypoglycaemia in four cases, dehydration (thirst, hypotension) in 12 cases. Four patients were hospitalized for acute adrenal insufficiency. Compared to patients who could fast the whole month, patients who stopped fasting had a more advanced age (49.3 years vs 47.1 years), more frequently a primary adrenal insufficiency (27% vs 17%) and a longer duration of the disease (10.6 years vs 8.7 years).
Conclusion
Fasting during Ramadan can be complicated especially in aged patients, a longstanding disease and a primary origin. More studies are needed and a consensus should be established for safe fasting in patients with adrenal insufficiency.

DOI: 10.1530/endoabs.37.EP83

EP84

Awareness of adrenal crisis prevention in long-term steroid users

Muhammad Ridhwaan Salehmohamed[1,2], Mark Griffin[2], Tom Branigan[2], Martin Cuesta[1,2] & Chris Thompson[1,2]
[1]Academic Department of Endocrinology and Diabetes Metabolism, Beaumont Hospital, Dublin, Ireland; [2]Royal College of Surgeons in Ireland, RCSI, Dublin, Ireland.

Background
Patients taking corticosteroids for immune suppression are vulnerable to adrenal crisis during intercurrent illness or if steroids are stopped abruptly. Although patients on glucocorticoids for adrenal failure are routinely provided with sick day rules, we wished to ascertain whether patients on immunosuppressive steroids are appropriately counselled.
Aim
This study sets out to compare patient awareness of steroid sick day rules in endocrine and non-endocrine patients.
Methods
A 9 point questionnaire to determine knowledge of steroid sick day rules was designed. 92 patients were consecutively recruited from non-endocrine clinics – respiratory ($n=22$), rheumatology ($n=24$), gastroenterology ($n=20$) and nephrology ($n=26$). 46 patients were consecutively recruited from the pituitary clinic. All patients completed the questionnaire.
Results
Endocrine patients exhibited better steroid awareness; they were more likely to double their steroid dose when ill (76.1% vs 6.5%), to obtain parenteral steroid during vomiting (82.6% vs 27.1%), and during surgery (87.0% vs 30.4%), and were aware of the need to carry a medicalert bracelet or a steroid-aware card (82.6% vs 20.7%), $P<0.001$ for all. However the endocrine patients were at par with the non-endocrine ones in terms of knowing the need to inform their doctor of being on steroid (91.3% vs 88.0%).
Conclusion
Endocrine patients exhibited a significantly greater knowledge of precautions for steroid use. The data does highlight the lack of patient awareness of the sick day rules in patients on immunosuppressive therapy for non-endocrine conditions. Endocrinologist could assist colleagues in other specialities in awareness of steroid sick day rules.

DOI: 10.1530/endoabs.37.EP84

EP85

Subclinical Cushing's syndrome: report of 17 cases

Faten Haj Kacem, Nesrine Cheikhrouhou, Nadia Charfi, Najwa Lassoued, Fatma Mnif, Mouna Mnif, Nabila Rkik & Mohamed Abid
Department of Endocrinology, Hedi Chaker Hospital, Sfax, Tunisia.

Introduction
Subclinical Cushing's syndrome refers to autonomous cortisol secretion in patients who do not have the typical signs and symptoms of hypercortisolism. This study was undertaken to describe clinical, biological and radiological features of this disease and to evaluate the clinical outcome after surgical and medical treatment.
Methods
Retrospective study conducted over a period of 12 years and including 17 patients hospitalised in our department of endocrinology for subclinical Cushing's syndrome.
Results
The average age of our patients was 58.94 years (38–77) with a sex ratio (M/F) of 1.12. The average waist circumference was 99.05 cm (range: 80–134). Obesity was found for 46% of patients, overweight for 54% of patients. The response of dexamethasone suppression test (2 mg) was altered for all patients. Urinary free cortisol was dosed for four patients (23.5%), normal in three cases (75%) and high in one case (25%). The mean level of ACTH was 20.21 ng/l (10–39.7). The adrenal CT showed an unilateral adenoma for 82%, bilateral adrenal hyperplasia for 12% and two right adrenal adenoma for 6% of cases. The repercussions of subclinical Cushing's syndrome were HTA for 47.05%, dyslipidaemia for 23.5%,

diabetes for 23.52%, impaired glucose tolerance for 29.41%, metabolic syndrome for 41.17%, obesity for 46% and hypokalaemia for 11.7% of cases. 58.8% of patients were operated, 50% of them presented adrenal insufficiency, all patients presented an improvement of anthropometric parameters and regression dyslipidaemia. 33% presented an improvement in hypertension and 28.57% presented a regression of diabetes. Conservative management was decided for 23.52% of patients, their evolution, with a mean follow of 4.75 years (3–7), showed an aggravation of diabetes for 50% and aggravation of dyslipidaemia for 50% of cases. No one presented an evolution to a Cushing. 17.64% were lost of follow up.

Conclusion

Adrenal surgery appears to be beneficial in case of pre-Cushing' syndrome for both metabolic and cardiovascular complications.

DOI: 10.1530/endoabs.37.EP85

EP86

Challenges in a the management of adrenal Cushing's syndrome associated with bilateral adrenal tumours and uterine leiomyoma

Catalina Poiana[1,2], Mara Carsote[1,2], Adriana Gruia[3], Dan Peretianu[4], Ermina Gheorghiu[2], Rodica Petris[3], Sorin Paun[1,5], Anda Dumitrascu[2] & Dan Hortopan[2]

[1]C. Davila University of Medicine and Pharmacy, Bucharest, Romania; [2]C.I.Parhon National Institute of Endocrinology, Bucharest, Romania; [3]Medlife Medical Centre, Bucharest, Romania; [4]SCM Povernei Medical Centre, Bucharest, Romania; [5]Floreasca Emergency Hospital, Bucharest, Romania.

Introduction

The Cushing's syndrome associated bilateral adrenal tumours comprise a wide area of diagnosis; the therapeutic approach is challenging since unilateral intervention might involve persistent hypercotisolemia, and bilateral adrenalectomy induces chronic adrenal insufficiency. The adrenal vein catheterism is not available in many countries.

Case report

50-year old non-smoker female has the following medical history: 2 years ago she presented to endocrinology because of weight gain with android features. On admission, diabetes mellitus and high cholesterol were found. The plasma ACTH was low (of 3 pg/ml), and the 2 mg of 2 days dexametasone suppression test showed no suppression of plasma morning cortisol. The computed tomography showed a right adrenal tumour of maximum 3 cm diameter and a smaller left adrenal tumour. Laparoscopic right adrenalectomy was performed. After surgery, no sign of adrenal insufficiency was found, so no glucocorticoid substitution was necessary. The blood levels remained normal. Six months after surgery, the morning plasma cortisol after 2 mg or 2 days dexametasone was 1.13 μg/dl. After six more months, the patient accused asthenia, and presented hemorrhagic diathesis as skin bruising, and three episodes of menopausal metrorrhagia. Also, the Cushing syndrome was suspected, the adrenal axes remained normal (morning cortisol of 11.9 μg/dl, ACTH of 7 pg/ml) but the left adrenal tumour increased at 4 cm maximum diameter; the pelvic ultrasound revealed an uterine leiomyoma of 2.82 cm. Endometrial haemostasis was performed by biopsy. 18 months after surgery the patient felt well, and the dexamethasone suppression test was still normal. Close follow-up is necessary.

Conclusion

Unilateral adrenalectomy in the bilateral adrenal tumours underling Cushing's syndrome may involve the syndrome remission but life follow-up is necessary because the risk of syndrome relapsing (in case of bilateral macronodular hyperplasia); the lack of adrenal insufficiency after first intervention is the marker of bilateral involvement.

DOI: 10.1530/endoabs.37.EP86

EP87

Spectrum of presentation and aetiology of adrenal haemorrhage: a case series

John Joseph McCabe[1], Colm Mac Eochagain[1], Donal O'Connor[2], James Gibney[1,3], Kevin Conlon[2] & Mark Sherlock[1,3]

[1]Department of Endocrinology, Adelaide and Meath Hospital incorporating the National Children's Hospital, Tallaght, Dublin, Ireland; [2]Department of Upper Gastrointestinal and Hepatobiliary Surgery, Adelaide and Meath Hospital incorporating the National Children's Hospital, Tallaght, Dublin, Ireland; [3]Department of Endocrinology, Trinity College, Dublin, Ireland.

Introduction

Adrenal haemorrhage is rare. There is a broad spectrum of clinical presentation and aetiology of the condition making it challenging to diagnose. Endocrine dysfunction frequently complicates cases of adrenal haemorrhage. Failure to recognise the condition or its complications can lead to devastating consequences for the patient.

Methods

All patients referred to our centre with adrenal haemorrhage between 2004 and 2014 were included in this retrospective study. The clinical notes, laboratory & radiological investigations of each case were recorded.

Results

Ten patients with adrenal haemorrhage were identified. Seven patients presented with acute abdominal pain. Adrenal haemorrhage was an incidental histological finding in two patients and an incidental radiological finding in one patient. Three of ten patients were diagnosed with hypoadrenalism. Six of ten patients underwent elective adrenalectomy following haemodynamic stabilisation with no associated operative mortality.

Conclusion

The aetiology of adrenal haemorrhage is variable and identifying the underlying diagnosis can be challenging. The appropriate management of the condition requires an awareness of the potential endocrinological consequences of adrenal dysfunction including glucocorticoid deficiency and catecholamine hypersecretion. In our centre elective adrenalectomy following endocrine investigations and haemodynamic stabilisation rather than emergency adrenalectomy is preferred. In this series there was no operative mortality associated with this approach, which is recognised as being elevated in patients operated on acutely for adrenal haemorrhage.

DOI: 10.1530/endoabs.37.EP87

EP88

A single-centre 10-years experience with pasireotide in Cushing's disease: patients characteristics and outcome

Laura Trementino[1,2], Grazia Michetti[1,2], Alessia Angeletti[1,2], Giorgia Marcelli[1,2], Carolina Concettoni[1,2], Marina Cardinaletti[1,2], Barbara Polenta[1,2], Marco Boscaro[1,2] & Giorgio Arnaldi[1,2]

[1]Division of Endocrinology, Polytechnic University of Marche, Ancona, Italy; [2]Endocrinology Unit, Department of Medicine DIMED, University-Hospital of Padua, Padua, Italy.

Introduction

Pasireotide is the first pituitary-directed drug approved for Cushing's disease (CD). We report our 10-years experience with pasireotide in CD reviewing and analysing data about all the patients treated with pasireotide at our referral centre both in randomised trials and in clinical practice.

Patients and methods

Twenty active CD patients were treated. Fourteen patients were treated with pasireotide in randomised trials and six patients were treated with pasireotide s.c. (Signifor; Novartis AG) in clinical practice. The mean treatment duration was 20.5 months (median 9 months; range, 3–72 months). The mean daily s.c. dose was 1333 μg (range, 1200–1800 μg) at the beginning of treatment as well as 1366 μg at last follow-up (range, 600–2400 μg).

Results

Urinary free cortisol (UFC) levels mean percentage change ($\pm$S.D.) at last follow-up was –40.4% ($\pm$35.1; range, 2–92%; median reduction 33.3%) with a normalisation rate of 50% (10/20). UFC normalisation occurred by months 1–3 in the majority of patients (8/10; 80%). Ten patients achieved sustained normalised late night salivary cortisol (LNSC) levels during treatment. LNSC normalisation was associated with UFC normalization (7/10 patients). Serum cortisol and plasma ACTH significantly decreased from baseline to last follow-up. Body weight decrease and blood pressure improvement during treatment were independent from UFC response. Glucose profile worsening was observed in all the patients except one. The frequency of diabetes increased from 40% (8/20) at baseline to 85% (17/20) at last follow-up requiring to start medical treatment only in a half of patients (8/17).

Conclusions

Pasireotide treatment was associated with sustained biochemical and clinical benefit in about 50% of CD patients. Glucose profile alterations are a frequent complication of pasireotide treatment however this adverse event seems to be easy to manage with diet and lifestyle intervention in almost half of patients.

DOI: 10.1530/endoabs.37.EP88

EP89

Low DHEAS: a sensitive and specific screening test for the detection of subclinical hypercortisolism in adrenal incidentalomas

Michael Conall Dennedy[1,4], Anand K Anamalai[1], Olivia Prankerd Smith[1], Andrew S Powlson[1], Johann Graggaber[1], Ashley Shaw[2], David J Halsall[3] & Mark Gurnell[1]
[1]Metabolic Research Laboratories, Institute of Metabolic Science, Addenbrooke's Hospital, University of Cambridge and National Institute for Health Research Cambridge Biomedical Research Centre, Cambridge, UK; [2]Departments of Radiology, Addenbrooke's Hospital, University of Cambridge and National Institute for Health Research Cambridge Biomedical Research Centre, Cambridge, UK; [3]Departments of Clinical Biochemistry, Addenbrooke's Hospital, University of Cambridge and National Institute for Health Research Cambridge Biomedical Research Centre, Cambridge, UK; [4]Discipline of Pharmacology & Therapeutics (MCD), National University of Ireland, Galway, Galway, Ireland.

Subclinical hypercortisolism (SH) occurs in 5–30% of incidentally-detected adrenal adenomas (AIs). Common screening tests for ACTH-independent hypercortisolism have significant false positive rates, mandating further investigations that are both time and resource intensive. We investigated whether a low basal DHEAS level is a sensitive and specific screening test for the detection/exclusion of SH in patients with newly-diagnosed AI. We recruited 185 consecutive patients with AI referred to our clinic between 2006 and 2013 were screened for clinical and biochemical evidence of adrenal medullary and cortical (1 mg dexamethasone suppression test, 24 h urinary free cortisol (UFC), serum DHEAS, plasma renin and aldosterone) hyperfunction. All positive dexamethasone suppression (>1.8 μg/dl (50 nmol/l)) and UFC ($>$ upper limit of reference range) results were further investigated, and we diagnosed SH when at least two of the following criteria were met: raised UFC, raised midnight serum cortisol, 48 h dexamethasone suppression test cortisol >1.8 μg/dl (50 nmol/l). Plasma ACTH was <10 pg/ml (2.2 pmol/l) in all patients with SH. At presentation, 29 patients (16%) were diagnosed with SH. We calculated an age-and gender-specific DHEAS ratio (derived by dividing measured DHEAS by the lower limit of the respective reference range) for all patients in the cohort and found that a ratio ≤ 1.12 was a sensitive (100%) and specific (91.9%) screening test for the diagnosis of SH. In comparison, a cortisol level after a 1 mg dexamethasone suppression test of 1.9 μg/dl (53 nmol/l) was a sensitive (100%) screening test for SH, but had lower specificity (82.9%). 24 h UFC lacked sensitivity (69%) and specificity (68%). A single basal measurement of DHEAS offers comparable sensitivity and greater specificity to the existing gold-standard 1 mg dexamethasone suppression test for the detection of SH in patients with AIs.

DOI: 10.1530/endoabs.37.EP89

EP90

Ultrasound importance in adrenal incidentalomas diagnostication and management

Yllka Themeli[1,2], Myftar Barbullushi[2,3], Aqif Gjokutaj[2,3], Gjergji Dilo[4] & Lindita Hoxha[4]
[1]'IKEDA' Hospital, Tirana, Albania; [2]DC 'Med.al', Tirana, Albania; [3]UHC 'Mother Teresa', Tirana, Albania; [4]DC 'Dermolife', Tirana, Albania.

Background
Adrenal incidentalomas are detected in about 0.1% of general health screening with ultrasound, in 0.4–1.9% among patients evaluated for nonendocrinologic complaints, in ~4.4% among patients who have a previous cancer diagnosis. Majority are benign, but careful evaluation is warranted to rule out carcinoma and functional adenomas.
Aim
The purpose of presenting these cases is to highlight the importance of ultrasound examination in diagnostication and management of adrenal incidentalomas.
Materials and methods
We have prescribed six patients presenting in our clinic during a 3-year period, which resulted with adrenal incidentaloma in abdominal ultrasound. They underwent specific blood tests, depending on the clinical situation.
Results
Case 1 was a 41-year old male, presenting with hyperglycemia found to have Conns' syndrome with aldosterone producing adenoma on routine ultrasound. Case 2 was a 21-year old boy, who had phaeochromocytoma misdiagnosed as anxiety disorders. Case 3 was a 49-year old female, presenting amenorrhoea which was mistaken as menopause, and minimal hirsutism which was mistaken as postmenopausal hirsutism. She resulted with adrenal androgen secreting adrenocortical carcinoma. Case 4 was a 59-year old hypertensive male, presenting with fever had phaeochromocytoma with catecholamine excess, producing fever. Case 5 was isolated adrenal tuberculosis, who presented with chronic diarrhea. Case 6 was a 43-year old female, presenting with drug-resistant hypertension and diabetes, found to have Cushing's syndrome.
Conclusion
Adrenal incidentalomas are common, most are non-secreting adenomas. When a hormonal disorder is suspected clinically, specific blood tests for Cushing, Conn and/or pheaochromocytoma, are indicated.

DOI: 10.1530/endoabs.37.EP90

EP91

RNALDO: the effects of blocker withdrawal on renin and angiotensin

Tomas Griffin[1,3], Gerard A Browne[1], Paula M O'Shea[2] & Michael Conall Dennedy[1,3]
[1]Discipline of Pharmacology & Therapeutics, NUI Galway, Galway, Ireland; [2]Department of Clinical Biochemistry, Galway University Hospital, Galway, Ireland; [3]Department of Endocrinology, Galway, Ireland.

Primary hyperaldosteronism (PHA) prevails in up to 20% of individuals with essential hypertension, but often presents a diagnostic challenge due to difficulty in interpreting the aldosterone renin ratio (ARR) largely due to anti-hypertensive medication interference. Interpretation of the ARR in the context of beta blockers presents a particular challenge and may produce false positive results due to renin suppression. We investigated the effects of beta blocker withdrawal on ARR in a cohort taking long term beta blocker therapy for blood pressure (BP) control. Hypertensive individuals with suboptimally controlled BP on a combination of beta blockers, thiazide diuretics and ACEi/ARB were recruited and followed over 8 weeks. Beta blockers were withdrawn at the first visit. Serial measurements of BP were performed and patients had blood drawn serially for measurement of plasma renin activity (PRA), renin mass, aldosterone and electrolytes. BP was optimised at each visit by maximising non-renin-suppressing antihypertensive agents. Main outcome measures were ARR, renin and aldosterone concentrations following beta-blocker withdrawal. 50 individuals were enrolled under informed consent and ethical approval. Interpretation of ARR on beta-blockade gave a false positive diagnosis of PHA in 22%. Beta blocker withdrawal produced a rapid (>50%) recovery of PRA ($F=28.6$; $P<0.0001$) and renin mass ($F=18.4$; $P=0.0007$) which reached significance within 2 weeks of withdrawal and return of the ARR to normal range in all individuals ($F=29.3$; $P=0.0003$). Aldosterone remained unchanged throughout the duration of the study ($F=2.5$; $P=0.1$). BP remained unchanged throughout the duration of the study ($F=1.0$; $P=0.4$). Both renin mass ($r^2=0.67$; $P<0.05$) and PRA ($r^2=0.69$; $P<0.05$) were inversely correlated with beta blocker dose. While clean screens using the ARR are seldom possible, our results demonstrate a high false positive rate for PHA in those taking beta blockers. Beta blocker withdrawal was well tolerated, BP control easily optimised and the ARR more accurate within 2 weeks of withdrawal. We provide convincing data to support beta blocker withdrawal, 2 weeks in advance of screening for PHA.

DOI: 10.1530/endoabs.37.EP91

EP92

Long-term outcome from unilateral adrenalectomy in patients with primary aldosteronism

Mark J Hannon, Candy Sze, Robert Carpenter, Laila Parvanta, Matthew Matson, Anju Sahdeve, Maralyn R Druce, Mona Waterhouse, Scott A Akker & William M Drake
St Bartholomew's Hospital, London, UK.

Primary aldosteronism (PA) is an important cause of hypertension which confers significant cardiometabolic risk. In approximately half of cases, the cause is a surgically resectable unilateral aldosterone-producing adrenal adenoma, making PA the most common potentially curable form of hypertension. Despite this, long-term data on surgical outcomes that could be used to guide discussions with patients are sparse. Here, we report on clinical outcomes several years post-adrenalectomy in those patients from our prospectively studied cohort who underwent surgery.
Of 120 consecutive patients investigated for PA, 51 underwent laparoscopic-assisted adrenalectomy. Blood pressure, number of antihypertensive medications, and serum potassium were recorded before adrenalectomy, and at the time of most recent follow-up. Recumbent renin and aldosterone were measured ≥ 3 months after surgery, to determine if PA had been biochemically cured. This was performed in the absence of interfering antihypertensive medication, and with oral potassium supplementation given as necessary.

The cohort consisted of 31 males and 20 females, median age 54 (range 30–83). Median duration of follow up was 48 months (range 3–154). Median pre-operative blood pressure (on medication) was 160/95 (range 120/80–250/150). Overall, blood pressure significantly improved post-operatively, to a median of 130/80 (range 110/70–160/93, $P<0.0001$). Median serum potassium level increased from 3.2 mmol/l pre-operatively (range 2.3–4.7) to 4.4 mmol/l post-operatively (range 3.3–5.3, $P<0.0001$). Median number of antihypertensive medications used improved from median 3 pre-operatively to median 1 post-operatively ($P<0.0001$). 3/51 patients (5.9%) did not achieve any improvement in blood pressure post-operatively; however, histological examination of these patients' removed adrenal glands confirmed the presence of fully excised, typical Conn's adenomas in each case.

Laparoscopic-assisted unilateral adrenalectomy provides excellent long term improvements in blood pressure control, polypharmacy, and hypokalaemia. These data may help inform discussions with patients about possible surgical outcomes.

DOI: 10.1530/endoabs.37.EP92

EP93

Phaeochromocytoma-the Mater hospital experience over the past two decades

Bernadette Monaghan, Sinead Egan, Gerry McEntee & Maria Byrne
Mater Misericordiae University Hospital, Dublin, Ireland.

Phaeochromocytoma is a rare neuroendocrine tumour. Incidence has been quoted at two to eight cases per million people. This study reviews all cases of surgically resected phaeochromocytoma in a large tertiary referral centre since 1996 with particular focus on preoperative care. 22 patients were diagnosed with Phaeochromocytoma with average age at diagnosis of 47 years. 13.6% ($n=3$) of patients had malignant phaeochromocytoma. Two patients had confirmed neurofibromatosis Type 1. The remaining cases were deemed sporadic and are awaiting genetic analysis. In terms of pre-operative optimisation, medical treatment involves alpha blockade initially +/− beta blockade if tachycardic. It took 9.7 ± 8.2 days on average to obtain adequate alpha blockade. The mean dose of phenoxybenzamine used was 88.1 ± 74.1 mg. The mean preoperative blood pressure on the day of surgery was $122/71\pm19/12$ mm/Hg. The average postoperative blood pressure which was measured in recovery was $109/63\pm15/10$ mm/Hg. The mean heartrate pre-operatively was 74 ± 16 bpm corresponding with a postoperative value of 75 ± 14 bpm. Of the 22 patients that underwent surgical resection, 81.8% of patients ($n=18$) required ITU/HDU care post-op with an average length of stay of 3.1 ± 1.6 days. 50% ($n=11$) required inotropic support post-op for an average of 1.9 ± 1.1 days. In terms of immediate post-op complications, hypotension was the most common. One patient (known catecholamine induced cardiomyopathy) developed a cardiac arrest during anaesthesic induction. There was one case of post op hypertension requiring nitrate infusion. Mortality related to surgery was nil. One patient has died secondary to complications of metastatic phaeochromocytoma, the other patient died of an unrelated condition. In the 22 cases described, each presented a unique set of management challenges. This report showed that once diagnosed, intensive medical stabilisation is required to prevent adverse surgical outcomes.

DOI: 10.1530/endoabs.37.EP93

EP94

Combined effects of sirolimus and mitotane in the inhibition of growth in human adrenocortical carcinoma cells

Maria Cristina De Martino[1,2], Peter M van Koetsveld[1], Richard A Feeldes[1], Steven W J Lamberts[1], Wouter W de Herder[1], Annamaria Colao[2], Rosario Pivonello[2] & Leo J Hofland[1]
[1]Division of Endocrinology, Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands; [2]Dipartimento di Medicina Clinica e Chirurgia Endocrinologia e Metabolismo Università degli Studi di Napoli Federico II, Naples, Italy.

Adrenocortical cancer (ACC) is a rare cancer with poor prognosis and scant treatment options. Mitotane alone, or in combination with cytotoxic chemotherapy, represents the referral current treatment for patients with unresectable ACC. Recent studies have shown that mTOR inhibitors suppress growth of ACC cells. This study aimed at evaluating the effects of mitotane in combination with mTOR inhibitors. In H295 and SW13 cells we tested the effects of a 6 day treatment with increasing doses of mitotane in the presence or absence of selected doses of sirolimus on cell proliferation as measured by the total DNA content. The tested doses of mitotane ranged between 10^{-7}–10^{-5} M in both H295 and SW13 cells, sirolimus was tested at concentrations of 5×10^{-9} and 10^{-6} M in H295 and 5×10^{-11} and 10^{-10} M in SW13. In H295, mitotane significantly inhibited cell proliferation at all concentrations tested, with an IC50 of 4.5×10^{-6} M and a maximal inhibition of 87% as compared with vehicle-treated controls ($P<0.001$). In SW13, mitotane significantly inhibited cell proliferation at concentrations higher than 2.5×10^{-6} M, with an IC50 of 1.6×10^{-5} M and a maximal inhibition of 81% as compared with vehicle-treated controls ($P<0.001$). In both H295 and SW13 sirolimus significantly inhibited cell proliferation at both concentrations tested and when combined with mitotane, it showed statistically significant additive effects. This additivity was observed only with low mitotane doses (between 10^{-7} and 5×10^{-6} M). Using mitotane doses higher than 5×10^{-6} M the cell proliferation inhibition was already nearly maximal and no significant additive effects could be observed. The current study demonstrates that sirolimus has additive antiproliferative effects when combined with low mitotane doses. These doses correspond to concentrations lower than the therapeutic range of mitotane. If this effect can also be achieved *in vivo* our data suggest that the addition of sirolimus to mitotane might be useful in ACC patients when the therapeutic range of mitotane range is not reached.

DOI: 10.1530/endoabs.37.EP94

Steroids, development and paediatric endocrinology

EP95

Linear growth and endocrine function in patients with ataxia telangiectasia; a cohort of 13 patients in Qatar

Mohammad Ehlayel[1,2] & Ashraf Soliman[1,2]
[1]Hamad Medical Centre, Doha, Qatar; [2]Weill Cornell Medical College, Doha, Qatar.

Introduction

Ataxia telangiectasia (AT) is a rare, genetic, primary immune deficiency disease characterised by immunodeficiency and neurological manifestations, with increased tendency to infection, malignancy, and autoimmune diseases. Both growth delay and endocrine abnormalities are occasionally reported in these patients.

Aim

To study linear growth in relation to endocrine and immune functions in a cohort of children with AT.

Patients and methods

We studied growth parameters (height (Ht), weight, BMI and measured the HtSDS) of 13 patients (age 7.7 ± 3.5 years) with AT in relation to their mid-parental HtSDS. We measured their biochemical (serum calcium (Ca), phosphorus (PO_4), alkaline phosphatase (ALP), alanine transferase (ALT), ferritin, creatinine and albumin), endocrine (free thyroxine (FT_4), TSH, IGF1, 8 AM cortisol) and immune functions (IgG, IgM and IgA antibodies). Growth data were correlated to hormonal and immune data.

Results

Presented in table.

	HtSDS	BMI (kg/m^2)	MPH-tSDS	IGF1 (μg/l)	FT_4 (pg/ml)	TSH (mIU/l)	Anti TPO (U/ml)	Albumin (g/l)	ALT (U/l)	Ferrtin (μg/l)
Mean	−1.4	15.1	−1.3	149.0	15.2	7.3	88.7	39.2	42.2	324.0
SDS	1.2	2.4	1.1	110	3.8	13.6	131	7.2	24.2	606.3
No=	13.0	13.0	13.0	8.0	13.0	13.0	13.0	13.0	13.0	9.0
Abnormal	22%	31%	38%	31%	38%	15%	31%	15%	15%	38%

All patients had normal renal function. Thirty-one percent of patients with AT had short stature (HtSDS <-2). However, their MPHtSDS denoted that their short stature is familial as 4/13 had MPHtSDS <-2. They had low BMI and two of them had low serum albumin and IGF1 denoting malnutrition. Low IGF1 (IGF1 SDS <-1.5) can be explained in part by under- nutrition or disturbed GH secretion. Elevated serum ALT and ferritin in some patients suggest immune-related inflammation in the liver. Thirty percent of patients had high TSH, two of them had low FT_4 diagnosing clinical (15%) and sub-clinical (15%) hypothyroidism. Anti-peroxidase antibodies were high in 2/13 denoting immune-related thyroid aggression. 8/13 had vitamin D deficiency (<20 ng/ml) however, their serum Ca and PO_4 levels were normal. One adolescent girl (14.5 years) had hyper-gonadotropic hypogonadism (low estradiol and high FSH) All patients had normal AM cortisol. None of the growth parameters were correlated with the immunoglobulin (IgG, IgM or IgA) levels.

Summary
Patients with AT had high prevalence of growth delay and endocrine dysfunction in the form of low IGF1 clinical and subclinical hypothyroidism and hypogonadism. Early diagnosis and management of these endocrinopathies is important or improving the prognosis of the disease.

DOI: 10.1530/endoabs.37.EP95

EP96

Abstract withdrawn.

DOI: 10.1530/endoabs.37.EP96

EP97

Unusual presentation of the apparent mineralocorticoid excess, triggered by mild Cushing's disease in an adult

Andrej Zavratnik[1], Matej Zavrsnik[1], Urska Ksela[1], Evgenija Homsak[1], Antonela Sabati Rajic[2], Damien Gruson[3] & Marija Pfeifer[2]
[1]Univeersity Clinic Centre Maribor, Maribor, Slovenia; [2]University Medical Centre Ljubljana, Ljubljana, Slovenia; [3]Cliniques Universitaires St-Luc and Université Catholique de Louvain, Brussels, Belgium.

Introduction
The syndrome of apparent mineralocorticoid excess (AME), a genetic disorder, resembles findings similar to those in primary aldosteronism, but aldosterone levels are low. AME is due to deficiency in the 11-beta-hydroxysteroid-dehydrogenase-enzyme-type-2 isoform (11-beta-HSD2), which normally converts cortisol to cortisone to prevent its mineralocorticoid activity at the aldosterone-sensitive sites. The deficiency in 11-beta-HSD2 leads to marked elevation in net mineralocorticoid activity caused by unconverted cortisol.
Case report
50-years old woman was hospitalised after collapse. She had had arterial hypertension for 10 years (bisoprolol 5 mg/day, perindopril/indapamide 8/2.5 mg/day). At the presentation she was hypotensive 96/64 mmHg, mildly Cushingoid, BMI 28 kg/m^2. Initial laboratory results: s-K 2.44 mmol/l, spot u-K 56 mmol/l, blood pH 7 440. Patient's medical records revealed, that hypokalaemia had developed after 2001 and had been worsening gradually. After correction of hypokalaemia primary aldosteronism was excluded (PRA 0.015 nmol/l, aldosterone 0.22 nmol/l, after saline infusion aldosterone suppressed to 0.08 nmol/l). Cushing's disease was confirmed (s-ACTH: 5.31 pmol/l, cortisol after standard 2-day 2-mg dexamethasone test: 213 nmol/l, late evening cortisol: 157 nmol/l, pituitary MRI: 3×4 mm microadenoma, IPSS: a central-to-peripheral plasma ACTH-gradient of 17.5, and left to right ACTH-ratio of 2.37 before CRH administration). Since mild Cushing's disease couldn't explain severe hypokalaemia additional underlying cause was suspected. After exclusion of licorice ingestion and adrenocortical tumour, the AME was confirmed by undetectable free-cortison levels in urine measured by liquid-chromatography–tandem mass-spectrometry in two consecutive 24-h urine samples (free cortisol 60.44 and 61.27 nmol/l, free cortison two-times undetectable). Spironolactone was introduced. With the dose of 150 mg/day the patient is normokalaemic, and the hypertension is well controlled by additional bisoprolol 5 mg/day and perindopril 4 mg/day.
Conclusion
11-beta-HSD2 deficiency is a rare cause of hypertension and hypokalaemia. Presented case report is of special interest showing that mild Cushing's disease has unmasked the underlying enzyme deficiency. Genetic testing is in progress. Transsphenoidal microadenomectomy is planned.

DOI: 10.1530/endoabs.37.EP97

EP98

Evaluation of β-oestradiol induced DNA damage in the leukocytes of young, elderly and Alzheimer's disease patients in the comet assay

Lada Zivkovic[1], Biljana Spremo-Potparevic[1], Ninoslav Djelic[2] & Vladan Bajic[3]
[1]Department of Physiology, Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia; [2]Department of Biology, Faculty of Veterinary Medicine, University of Belgrade, Belgrade, Serbia; [3]Department of Radiobiology and Molecular Genetics, Institute for Nuclear Sciences 'Vinca', University of Belgrade, Belgrade, Serbia.

Oestrogen has very complex effects on the CNS. It protects neurons from noxious effects of β amyloid *in vitro*, ameliorates the cerebral metabolism and increases the level of acetylcholine in the basal forebrain and hippocampus. Its beneficial impact in Alzheimer disease may be attributed in part to its antioxidant activity. On the other hand, it has been demonstrated that oestrogens may exhibit genotoxic effects, especially at elevated tissue concentrations. Therefore, the aim of the present investigation was to determine wether oestradiol induces DNA damage in whole blood leukocytes from healthy young females and males, healthy elderly females and males and females and males with Alzheimer disease. All experiments were performed using the alkaline version of the Comet assay (single cell gel electrophoresis). Cell viability was determined by Trypan blue exclusion assay. A significant increase of DNA migration in the Comet assay was observed in leukocytes of all treated groups (young and elderly females, young and elderly males, females and males with Alzheimer disease) at all concentrations of oestradiol (50, 100 and 250 μM) used in this investigation. In all experiments the cell viability was over 80%. Therefore, it can be concluded that leukocytes are sensitive to oestradiol in the Comet assay regardless of gender, age and health condition of examined subjects.

DOI: 10.1530/endoabs.37.EP98

EP99

Serum alanine aminotransferase and γ-glutamyltranspeptidase activities: new markers for polycystic ovary syndrome

Halime Kiliç[1], Fatma Aydin[2], Burak Uz[3], Feridun Karakurt[4], Mustafa Koroglu[5] & Ayse Kargili Carlioglu[6]
[1]Nenehatun Hospital of Gynecology and Obstetrics, Erzurum, Turkey; [2]Department of Gynecology and Obstetrics, Şifa Hospital, Erzurum, Turkey; [3]Department of Hematology, Fırat University Medical School, Elazig, Turkey; [4]Department of Endocrinology, Selçuk University Medical School, Konya, Turkey; [5]Department of Hematology, Karaelmas University Medical School, Zonguldak, Turkey; [6]Department of Endocrinology, Erzurum Regional Training and Research Hospital, Erzurum, Turkey.

Objective
Polycystic ovary syndrome (PCOS) is associated with insulin resistance, central obesity and dyslipidaemia. Furthermore, abnormal aminotransferase activity is common in women with polycystic ovary syndrome. The aim of this study is to assess the γ-glutamyltranspeptidase (GGT) and alanine aminotransferase (ALT) levels in women with PCOS in whom non-alcoholic fatty liver disease was excluded by history, serum testing and abdominal ultrasonography.
Study design
Present work is included 135 consecutive outpatient between January and July 2006. Ninety patients for the diagnosis of PCOS and 45 age-matched healthy subjects in the control group. Women with PCOS were separated into two groups. Group A were treated with 0.035 mg of Ethinyl Oestradiol and 2 mg of cyproterone acetate for 6 months. Group B did not take any drug. Serum levels of ALT, as-partat aminotransferase (AST), GGT, alkaline phosphatase (ALP), lipid and glucose metabolism parameters were measured on the 6th month of treatment.
Results
The plasma levels of both ALT and GGT were significantly higher in the subjects with PCOS (total) compared to the controls. Serum GGT levels were significantly higher in the group A and B than in controls, whereas no difference was found between group A and B. On the other hand group B had significantly higher ALT levels than in controls. However, no differences in ALT levels were found between group A and controls.

Conclusions
The ALT and/or GGT levels are important in the pathogenesis of PCOS and that hepatic enzymes may be useful additional measures in identifying women at high risk of metabolic syndrome.

DOI: 10.1530/endoabs.37.EP99

EP100

Achievement of therapy targets in children and adolescents with type 1 diabetes mellitus at the 'Diabetes School'

Akmaral Tashmanova[1,2]
[1]Center for the Scientific and Clinical Study of Endocrinology, Tashkent, Uzbekistan; [2]Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan.

Aim
To assess efficacy of training and achievement of therapy targets in children and adolescents with type 1 diabetes mellitus in 'Diabetes Schools'.
Materials and methods
The 5-day training course was conducted in 'Type 1 Diabetes School' at the Center for the Scientific and Clinical Study of Endocrinology, Uzbekistan Public Health Ministry (Tashkent). The training was conducted by means of a structured program containing all appropriate sections. Before and after training course all participants were tested with a questionnaire containing 30 key questions for self-control. On the basis of the findings children and adolescents with type 1 diabetes mellitus were divided into groups. 54 of 80 children and 38 of 57 adolescents were preliminary trained, 26 children and 19 adolescents got no training. DS5 Glycomat (USA) was used to measure HbA1c by means of high pH anion-exchange liquid chromatography. Certified by the National Glycohaemoglobin Standardization Program this method became the reference one. It helps demonstrate the predicting role of HbA1c level as a criterion for assessment of chronic glycaemia and achievement of therapy targets in children and adolescents with type 1 diabetes mellitus.
Results and discussion
Frequency of target HbA1c level ($\leq$7.5%) achievement in the trained patients was 68%. Among children who got no preliminary training target HbA1c level was found in 12%. Among trained adolescents 58% achieved compensation. The target HbA1c level was found in 11% of adolescents who got no training.
Conclusions
Frequency of target HbA1c level ($\leq$7.5%) achievement was found in 68% of children with type 1 diabetes mellitus having received preliminary training at 'Diabetes School' to be significantly higher ($P<0.001$) than the one in the group of patients who got no preliminary training (12%). Among adolescents target HbA1c level achievement was observed in 58% of the trained patients to be significantly higher ($P<0.001$) as compared with those who got no preliminary training (11%). Better compensation and higher frequency of target HbA1c level achievement in children as compared with those among adolescents confirms the role of family in the type 1 diabetes mellitus control.

DOI: 10.1530/endoabs.37.EP100

EP101

Interrelation between level of knowledge and type 1 diabetes mellitus compensation degree in children and adolescents

Akmaral Tashmanova[1,2]
[1]Center for the Scientific and Clinical Study of Endocrinology, Tashkent, Uzbekistan; [2]Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan.

Aim
To assess level of knowledge and compensation degree in children and adolescents with type 1 diabetes mellitus in "Type 1 Diabetes School".
Materials and methods
The 5-day training course was conducted in 'Type 1 Diabetes School' at the Center for the Scientific and Clinical Study of Endocrinology. The training was conducted by means of a structured program containing all appropriate sections. In total 137 children and adolescents with type 1 diabetes mellitus were included into the study. Among them 92 patients got training; 45 children and adolescents hospitalized at the Center for the Scientific and Clinical Study of Endocrinology got no training in the 'Type 1 Diabetes School'. DS5 Glycomat (USA) was used to measure HbA1c by means of high pH anion-exchange liquid chromatography.
Results and discussion
Study on efficacy of the training in the 'Diabetes School' by means of the questionnaire demonstrated that before training children with mean diabetes duration of 4.7 ± 1.8 years could give right answers to five or six questions only. Low-motivated children from low-motivated families with low level of knowledge who got no training were hospitalized at the intensive care unit more frequently both before and after training at 'Type 1 Diabetes School'. At follow-up they could give six or 11 right answers. Among trained adolescents with type 1 diabetes mellitus initially number of right answers was six, in 5 years they could give right answers to 19. Among the untrained adolescents level of knowledge was low both initially and after a 5-year follow-up. HbA1c level in the trained children after 5 years was found reduced by 2.4 ± 0.24% as compared with the initial one; it was reduced by 0.8 ± 0.3% in the untrained children. In trained adolescents with type 1 diabetes mellitus after 5 years HbA1c level reduced by 3.0 ± 0.36%; in those untrained the value was 2.3 ± 0.32%, but the adolescents did not achieved target HbA1c level.
Conclusions
Within a 5-year follow-up mean HbA1c level in the trained and untrained children was 7.8 and 10/8%, respectively. Among adolescents the values were 8.1 and 10.1%, respectively. Better compensation and higher frequency of target HbA1c level achievement in children as compared with those among adolescents confirms the role of family in the type 1 diabetes mellitus control.

DOI: 10.1530/endoabs.37.EP101

EP102

Influence of ecologically adverse factors on physical and sexual development of children living in the Aral Sea area

Nilufar Ibragimova & Feruza Hojaeva
Republican Specialized Research and Practical Medical Centre of Endocrinology, Tashkent, Uzbekistan.

Drying of the Aral Sea resulted in serious problems including pollution of air, water (mineralization of clear water) and soil which in its turn caused rise in various somatic diseases in population and produced a negative effect on health of children and adolescents.
Purpose
To study the influence of ecologically adverse factors on physical and sexual development of children of the Aral Sea area.
Materials and methods
To estimate physical and sexual development of adolescents of the Aral Sea area an epidemiological survey was carried out in 2008 using a method of random sampling considering age and sex. The study group comprised 1120 children (600 girls and 620 boys) aged 12 to 16. The study included anthropometry (coefficient of standard deviations SDS), BMI, estimation of sexual development (according to Tanner), USI of the small pelvis organs.
Results
Of 1220 children examined, stunting was found in 143 (11.7%) and weight deficiency in 67%. It should be noted that 85% of children were registered at the dispensary for anemia. The ratio of occurrence of stunting between boys and girls made 2:1. Of 620 boys examined stunting was found in 14.3%, sexual development retardation in 20% of boys, hypogonadism in 3%, obesity in 1.7%, micropenis in 2.5%, unilateral cryptorchism in 1.2%, other boys had normal for age puberty development. Of 600 girls examined stunting was revealed in 7.3%, abnormal puberty in 2.8%, retardation of sexual development in 12.8%, late menarche in 12.1% and primary amenorrhea in 4.3% of girls. Thus, the results obtained suggest on direct influence of adverse ecological factors (pollution of air, water, soil) of the Aral Sea area on health of children being confirmed with frequency of stunting (11.7%) in children and sexual development disorders revealed.

DOI: 10.1530/endoabs.37.EP102

EP103

Leptin and kisspeptin evaluation in childhood obesity

Francesco Leo[1], Antonio Mancini[1], Chantal Di Segni[1], Sebastiano Raimondo[1], Angelina Barini[2], Diego Currò[3] & Aurora Natalia Rossodivita[4]
[1]Department of Medical Sciences, Division of Endocrinology, Catholic University of Sacred Heart, Rome, Italy; [2]Institute of Biochemestry and Clinical Biochemestry, University of Sacred Heart, Rome, Italy; [3]Institute of Farmacology, University of Sacred Heart, Rome, Italy; [4]Department of Gynecology and Pediatrics, University of Sacred Heart, Rome, Italy.

Kisspeptin is a neuropeptide secreted in anteroventral-periventricular and arcuate hypothalamic nuclei involved pubertal onset and in other functions of adult life. Kisspeptin levels are sex dependent, so they are higher in prepubertal girls and in adult women compared to age-matched male. This sex-related pattern has been reported in adult obesity, but few data are reported in childhood obesity. In order to evaluate correlations between metabolic status and kisspeptin, we studied Kisspeptin levels in a population of 27 prepubertal children (13 males) aged 5–12 years, classified as overweight (n = 3) or obese (n = 24) according to Cole's criteria. Eight normal weight children, aged 6–12 years, were enrolled as controls. Several metabolic parameters were evaluated: glucose and insulin levels after oral glucose load, total- LDL- and HDL-cholesterol, triglycerides, uric acid, total proteins, C Reactive Protein. Leptin was evaluated using ELISA method (DRG Instruments GmbH, Germany). In order to evaluate kisspeptin levels, morning blood samples were collected; after acidification, peptides were extracted in a C-18 SEP-Column (Phenomenex, Inc., USA). The eluted samples were evaporated and stored at −80 °C until assayed. Kisspeptin (pg/ml) was measured using the RIA kit KISS1 (61-121)-Amide-Metastin (1-54)-NH2 (Phoenix Pharmaceuticals, Burlingame, USA). We did not find significant differences between obese and normal weight children (mean ± S.E.M: 20.1 ± 1.96 and 20.7 ± 0.68 pg/ml, respectively) and between males and females obese children (19.05 ± 3.39 and 20.9 ± 2.49 pg/ml). Kisspeptin levels did not correlate with SDS BMI, HOMA index and Insulin peak levels after glucose load. As expected, Leptin levels were higher in obese children than in controls (20.41 ± 2.84 and 4.21 ± 2 ng/ml, respectively), while showed a significant correlation with Kisspeptin levels in normal children ($R^2 = 0.12$; P value = 0.46), but not in obese ($R^2 = 0.03$; P value = 0.6). These preliminary data suggest that Kisspeptin could play a role in metabolic status and could be regarded as metabolic modulator and not only a regulator of pituitary gonadal axis.

DOI: 10.1530/endoabs.37.EP103

EP104

Kisspeptin hormone levels in girls and adolescent girls

Olga Gumeniuk, Yuriy Chernenkov, Natalia Zakharova & Inna Ivanenko
Saratov State Medical University, Saratov, Russia.

Kisspeptin (formerly known as metastin) is a neuropeptide, has an important role in initiating secretion of gonadotropin-releasing hormone at puberty. Kisspeptin hormone levels disorders cause hypogonadism or premature sexual development and sterility.

Aims

The study was undertaken to research the kisspeptin level in healthy girls and adolescent girls and in girls and adolescents with gynaecological and endocrine disorders.

Patients and methods

Serum kisspeptin levels were determined in 100 children and adolescents (aged 0.7–18 years). The healthy children was 12, children with precocious puberty (central precocious puberty CPP and premature isolated thelarche PIT) – 11, healthy adolescents – 30, girls with amenorrhea – 23, patients with polycystic ovary syndrome (PCOS) – nine and pregnant adolescent girls – 15. The concentration of kisspeptin was measured using Kisspeptin-10 and competitive enzyme immunoassay. Results were analyzed using two-way ANOVA. Data are expressed as median, P value of <0.05 was considered statistically significant.

Results

The investigation shows that healthy and pregnant adolescent girls had kisspeptin median levels 0.03 ng/ml. Among the girls with amenorrhea and PCOS kisspeptin levels were lower 0.01 ng/ml ($P = 0.014$). Serum kisspeptin levels were significantly higher in children with CPP and PIT and adolescent girls with PCOS than in control group (0.08 and 0.3 vs 0.03 ng/ml, $P = 0.012$ and $P < 0.01$).

Conclusion

Kisspeptin levels were various in healthy children, adolescents and girls with amenorrhe, PCOS, children with central precocious puberty and PIT. In this study, we demonstrated that serum kisspeptin levels were not different in healthy adolescents and pregnant adolescent girls. In this study, we demonstrated that serum kisspeptin levels were significantly lower in girls with amenorrhea and PCOS and higher in children with CPP and PT. The serum kisspeptin levels may be used as a marker of reproductive disorders and PCOS in girls.

DOI: 10.1530/endoabs.37.EP104

EP105

Clinical and endocrine features Hashimoto thyroiditis in children and adolescents

Slavica Markovic[1], Zoran Igrutinovic[2], Biljana Vuletic[2], Rasa Medovic[2] & Lidija Stankovic[2]
[1]Pediatric Clinic Clinical Centre Kragujevac, Kragujevac, Serbia; [2]Faculty of Medical Sciences Univerity of Kragujevac, Kragujevac, Serbia.

Introduction

Hashimoto's thyroiditis (HT) is the most common autoimmune thyroid disease and the most common cause of euthyroid goitre and acquired hypothyroidism in childhood.

Objective

To describe the clinical manifestations, course and outcome of HT in children and adolescents.

Method

The study included 43 patients with HT, aged 3–16 years, mean age 12.5 years, 36-girls, seven boys; 15 (35%) prepubertal, 28 (65%) pubertal, monitored on average of 4.9 years.

Results

Goitre is the most common symptom of HT, recorded in 19 (44.3%), and during follow-up in 31 (72%) of the children. In 17 (89.5%) were diffuse goitre, and in 15 (34.4%) children was isolated symptom. Goitre was recorded in 14 (73.7%) girls and 5 (21.3%) boys. Other clinical symptoms HT are: anaemia in seven patients (16.2%), fatigue in 5 (11.8%), increased appetite in 4 (9.7%), obtaining in TM 3 (7.0%), growth retardation in 2 children (4.7%) and irregular menstrual cycle in 5 (23.8%) out of 21 pubertal girls. Hypothyroidism is initially recorded in 7 (16.3%), and during follow-up the euthyroid state in 25 patients (58.1%). A positive family history of autoimmune thyroid disease had 18 (41.9%) children, of which 13 (72.2%) demonstrated hypothyroidism. In 12 (27.8%) children were identified: DMT1 in six children, vitiligo in two, M.Coeliacus in three, and M.Gravis in one child.

Conclusion

HT is five times more common among girls. The most common clinical symptom HT is a diffuse goitre, and hypothyroidism is recorded in 42%. The frequency of positive family history of autoimmune thyroid disease is high in children with HT, which increases the risk of developing hypothyroidism. As almost one-third of children with HT manifested and other autoimmune diseases, clinical follow-up involves the search for them.

DOI: 10.1530/endoabs.37.EP105

EP106

Neonatal screening for hypothyroidism in Romania

Ioana Ardeleanu[1,2], Michaela Nanu[1], Florentina Moldovanu[1] & Andrei Nanu[2]
[1]Mother and Child Health Care Institute 'Alfred Rusescu', Bucharest, Romania; [2]University of Medicine and Pharmacy 'Carol Davila', Bucharest, Romania.

Introduction

Neonatal screening is an effective method for early detection of congenital hypothyroidism, a disorder that requires the prompt initiation of the treatment, in order to prevent the subsequent neuropsychiatric impairments. Neonatal screening for hypothyroidism in Romania was initiated as a pilot project in 1979, has been expanded since 2002, and is currently conducted through the National Health Program funded by the Ministry of Health.

Objective

To assess the current state of hypothyroidism screening and management in Romania and determine the incidence of hypothyroidism at birth in 2013.

Material and methods

We analysed data reported to the Implementation Unit of Health Programs in 2013 by the four regional centres (Bucharest, Cluj, Iasi and Timisoara) and the parameters registered in the Hypothyroidism National Registry (in Bucharest and Iasi). Confirmed cases were treated and monitored by the endocrinology network. All the newborns were investigated by the 'dry spot' method; blood samples were collected from the heels. TSH levels were assessed by immunofluorimetric

method in three regional centres and by Elisa technique in the fourth. The diagnosis was locally confirmed by TSH, T_4 and free-T_4 levels in patients serum.
Results
In 2013, 92.76% of newborns were screened for hypothyroidism. 96 patients (0.07%) were found positive, when a neo-TSH cut-off value of 15 mU/l was used; in 41 newborns (0.03%) congenital hypothyroidism was confirmed. The family refused the diagnosis investigations in three patients (0.002%). The hypothyroidism incidence in this study is 1/3409 infants.
Conclusion
The incidence of congenital hypothyroidism in Romania is within the limits reported in literature. We attempt to increase the number of the newborns tested for hypothyroidism by raising awareness about screening benefit among the families. Taking into account the false positive cases, we estimate that ongoing studies will enable the increase of the neo-TSH cut-off value at 17 mU/l.

DOI: 10.1530/endoabs.37.EP106

EP107

Paediatric hypothyroidism: effect of thyroxin replacement therapy on growth hormone secretion and linear growth velocity

Sadia Saqib[1], Amjad Rashid Kiani[1], Urooj Anwar[1], Maleeha Akram[1], Gulbin Shahid[2], Osama Ishtiaq[3], Afzaal Ahmad[1], Mazhar Qayyum[1] & Shakeel Raza Rizvi[1]
[1]Department of Zoology Pir Mehr Ali Shah Arid Agriculture University Rawalpindi, Rawalpindi, Pakistan; [2]The Children's Hospital Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan; [3]Shifa International Hospital, Islamabad, Pakistan.

Thyroid gland secretes thyroid hormones, which play a critical role in growth, differentiation, reproduction and metabolism, whereas hypothyroidism in children is associated with short stature and normalisation of thyroid function with thyroxin replacement therapy increases linear growth velocity (LGV). In stimulating LGV, thyroxin may have its direct effects on bone cells or it may affect LGV through its effect on growth hormone (GH) secretion. The present study attempted to examine the effect of thyroxin replacement therapy on LGV in hypothyroid short children, its effect on GH secretion and the stage of puberty at which thyroxin replacement therapy could be more effective in influencing LGV. Blood samples were obtained and plasma T_3, T_4, TSH, GH and IGF-I were determined using specific assay systems. Data were analysed using Student's *t*-test and ANOVA. Twenty hypothyroid children (ten boys and ten girls) diagnosed on the basis of lower plasma levels of T_4 and T_3 and higher plasma concentrations of TSH, were given varying doses of thyroxin (16.6–150 μg/day for 12–36 months) administered orally at different ages (8–16 years) and stages (early, mid and late) of pubertal development. Following replacement therapy, children grew at a greater rate at higher doses of thyroxin. In addition, thyroxin replacement at early puberty in girls and at mid puberty in boys caused higher increases in LGV. The concentrations of GH and IGF-I increased significantly after treatment of hypothyroid patients with thyroxin. In conclusion, the present study demonstrates that hypothyroid children grow at a greater rate at higher doses of thyroxin and that thyroxin replacement therapy at early puberty in girls and mid puberty in boys causes higher increases in LGV. In addition, the current investigation indicates that increases in LGV following thyroxin replacement therapy are secondary to GH and subsequent IGF-I secretion.

DOI: 10.1530/endoabs.37.EP107

EP108

Evolution of the signs of true precocious puberty under suppressive treatment by LH RH analogues in girls

Ali El Mahdi Haddam[1], Nora Soumeya Fedala[2], Leyla Ahmed Ali[2], Djamila Meskine[1] & Farida Chentli[2]
[1]Bologhine Hospital, Algiers, Algeria; [2]Bab El Oued Hospital, Algiers, Algeria.

Introduction
Impact of suppressive therapy with LH RH analogues is more stop the premature pubertal development, reduce the acceleration of bone maturation that compromises the final size and avoid psychological disturbances caused by hormonal imbalance.
Aim
To study the effects of treatment on pubertal development, bone maturation and evolution of the size during and at the end of treatment and final height in 20 patients with central precocious puberty treated by triptorelin.
Subjects and methods
15 children (chronological age at diagnosis: 8 ± 1.8 years) at the end of treatment (11 ± 0.1 years) and the final size (15.9 ± 2.5 years) were treated for a central precocious puberty. The selection criteria for this study were treatment of central precocious puberty by Decapeptyl during 2 years or more. We assessed pubertal status, size and bone maturation at the beginning and the final size after stop taking treatment.
Results
At the beginning of treatment, pubertal development was S3 (S2–S4, size $+2.1 \pm 0.8$ DS/TC) and AO/10.5 ± 0.8 years. Under treatment, breast development decreased and bone maturation decelerated. The mean final height was 158.2 ± 6.6 cm; -1.5 ± 0.1 DS/TC.
Discussion and conclusion
Treatment of central precocious puberty by GnRH agonists stabilizes or regressed pubertal development and decreases bone maturation rate. However when indicated late, the prognosis size is not satisfactory.

DOI: 10.1530/endoabs.37.EP108

EP109

DHEA and its metabolites – daily profile

Monika Šrámková[1,2], Michaela Dušková[1], Luboslav Stárka[1], Beáta Racz[1] & Martin Hill[1]
[1]Institute of Endocrinology, Prague, Czech Republic; [2]First Faculty of Medicine, Charles University in Prague, Prague, Czech Republic.

Introduction
DHEA is a well-known neurosteroid. Its plasmatic level is reduced with ageing in most individuals. A non-negligible portion of DHEA is hydroxylated at C7 and C16 to 7α-, 7β- and 16α- and 16β-hydroxyderivatives. A part of the antiglucocorticoid function of DHEA has been described to its 7-oxygenated metabolites, namely to 7α-hydroxy-DHEA. Due its anti-glucocoticoid action it is also considered a factor in fat deposition processes. Thus, we were interested in examining daily profiles of DHEA and its metabolites, as well as possible associations with daily variation of hormones associated with food intake.
Description of methods
8 women of reproductive age with normal BMI were given five standardised meals, and their hormonal milieu was determined during the course of the day. Plasma from 12 withdrawals was analysed for DHEA and its 7- and 16-hydroxylated metabolites. The Ethical Committee of the Institute of Endocrinology approved the study.
Results
Free DHEA showed a small but significant decrease after lunch and dinner, whereas conjugated DHEA decreased only after dinner. Androstenediol decreased after lunch, but other changes were not significantly influenced by meals. 7α-hydroxy-DHEA and 3β,7α,17β-hydroxyandrostentriol followed the profile of DHEA, but 7β-isomer, 7-oxo-derivative and 3β,7β,17β-hydroxy-androstentriol did not. DHEA and all its derivatives showed an increase at 2200–2300 h, which, however, was significant only for free and conjugated DHEA, 7β-hydroxy-DHEA and 16α-hydroxy-DHEA.
Conclusion
The daily profile of DHEA levels shows a decrease throughout the day from the highest values in the morning value, with additional significant decreases after main meals. Only some hydroxylated metabolites and conjugated derivatives show a similar profile.
Disclosure
This work was supported by the grants ‐ NT12340, NT13890-4, NT11277-6 IGA MZCR and GAUK 1254314 Charles University, Prague.

DOI: 10.1530/endoabs.37.EP109

EP110

Aetiologies of thick stalks pituitaries: about 24 observations

Ali El Mahdi Haddam[1], Nora Soumeya Fedala[2], Leyla Ahmed Ali[2], Djamila Meskine[1] & Farida Chentli[2]
[1]Bologhine Hospital, Algiers, Algeria; [2]Bab El Oued Hospital, Algiers, Algeria.

Introduction
The inflammatoirs background processes, and infiltrating tumour of the pituitary stalk are rare. They are a heterogeneous group of lesions responsible of partial or global hypopituitarism.

Aim
Search for thickening of the pituitary stalk aetiologies and specify the clinical aspects.
Population methodology
This is a retrospective study of 24 patients with thickening of the pituitary stalk. All patients benefited from a clinical, biological and radiological exploration.
Results
A female predominance (17 women) with four paediatric cases are observed. The average age is 30 years (7–48). RMI was performed for hypopituitarism dissociated (*n*: 19); diabetes insipidus (*n*: 4) and early puberty (*n*: 1). The attainment of the stem is associated with a hyperprolactinaemia in 15 cases (62, 4%). Thyrotropin insufficiency in 16 cases (66.6%), gonadotropin insufficiency in ten cases (41.6%), corticotropin insufficiency in five cases (20, 8%), somatotropin insufficiency in four cases (16.6%) and central diabetes insipidus in four cases (16, 6%). The aetiological investigation led to the diagnosis of sellar metastasis in three cases (12, 5%), neurosarcoidosis in 15 cases (62.4%), autoimmune hypophysis in two cases (8, 3%) and germinoma in one child (4, 16%). Finally the aetiological investigation was negative in the remaining three cases (12.5%, two children).
Discussion and conclusion
The causes of thickening of the pituitary stalk are varied. They must be some thoroughly researched and monitored in idiopathic forms. La frequency of pituitary involvement encouraged to make regular hormonal evaluations.

DOI: 10.1530/endoabs.37.EP110

EP111

The beast behind the dwarf

Cosmina Rimbu[1], Lisandra Damian[1,2], Letitia Leustean[1,2], Ingrith Miron[2,3], Alexandru Florescu[2], Carmen Vulpoi[1,2] & Maria Christina Ungureanu[1,2]
[1]Endocrinology Clinic, 'St. Spiridon' Emergency Clinical Hospital, Iasi, Romania; [2]'Grigore T. Popa' University of Medicine and Pharmacy, Iasi, Romania; [3]Forth Pediatric Clinic, 'St. Maria' Hospital, Iasi, Romania.

Abnormalities of growth are one of the most common reasons for the paediatric–endocrinology consults. It's an obvious manifestation with countless possible causes behind, and sometimes we can have unexpected diagnosis.
Case presentation
we investigated the case of a 4 years old girl, born at term, naturally, SGA: birth weight = 1950 g, who presented in the Endocrinology Department for short stature. Clinical evaluation: 89.5 cm (−4 DS), 11 kg (−2.5 DS), discreet ocular asymmetry. Blood test: anaemia, decreased IGF-1, normal adrenal and thyroid function, normal karyotype, normal thoracic X-ray and abdominal ultrasound. Moreover, the first day of admission we noted polyuria and polydipsia not reported by mother: ingestion 3750 ml/24 h excretion 3950 ml/24 h. Afterwards, biochemical tests confirmed the suspicion of diabetes insipidus. Ophthalmologic exam – important papillary oedema. MRI revealed an expansive mass with contrast enhancement located in posterior fossa. An angio MRI and a biopsy were performed and established the final diagnosis: histiocytosis. Even if in our patient's case, the short stature and diabetes insipidus, were considered initially easy to manage and benign, the histiocytosis was found to be an unexpected and unpleasant diagnosis which involves more aggressive treatment and complications.

DOI: 10.1530/endoabs.37.EP111

EP112

Final size of turner patients: about 40 patients

Hafsa Siyoucef[1], Ali El Mahdi Haddam[1], Nora Soumeya Fedala[2], Djamila Meskine[1] & Farida Chentli[2]
[1]Bologhine Hospital, Algiers, Algeria; [2]Bab El Oued Hospital, Algiers, Algeria.

Introduction
The growth failure constant in turner syndrome is responsible for a spontaneous reduction in adult height with an average of 143 cm. Treatment with growth hormone has enhanced the stature prognosis.
Aim
Studying the final size of turner patients who have completed their growth.
Population, methodology
40 patients became adult patients were assessed on linear growth. The following factors were studied: The age and size at diagnosis, the introduction of treatment with GHr and the final size.
Results
The mean age at diagnosis was 8.9 ± 0.4 years, 45% over 10 years. The size at diagnosis was −4 DS/M and −3DS/TC. The age at initiation of treatment was 10 ± 0.1 years with a mean treatment duration of 5 ± 0.1 years. Ten patients were not able to be processed. Final height was −3, 5 DS/M and −2.5 S.D./TC with an average of 144 ± 0.2 cm for patients treated and −4DS/M and −4 DS/TC for the others.
Discussion and conclusion
Unfavourable results in our patients are explained by delayed diagnosis. Treatment may not be éfficace if the GHr treatment is not given precociously patient inflammatoirs background processes, and infiltrating tumour of the pituitary stalk are rare. They are a heterogeneous group of lesions responsible of partial hypopituitarism or global objective. Search for of thickening of the pituitary stalk aetiologies and specify the clinical aspects.

DOI: 10.1530/endoabs.37.EP112

EP113

Sarcopenia, more that dehydration, may be associate to underweight Portuguese centenarians

Alda Pereira da Silva[1,2], Andreia Matos[2,8], Ana Valente[5], Angela Gil[2,8], Isanete Alonso[6], Ricardo Ribeiro[2,7], Gorjão Clara[3,4] & Manuel Bicho[2,8]
[1]Alameda Primary Care Health Center, Lisbon, Portugal; [2]Faculty of Medicine, Genetics Laboratory and Environmental Health Institute – ISAMB, University of Lisbon, Lisbon, Portugal; [3]Universitary Geriatric Unit of Faculty of Medicine of Lisbon, University of Lisbon, Lisbon, Portugal; [4]Academic Medical Center of Lisbon – North of Lisbon Hospital Center, Lisbon, Portugal; [5]Department of Nutritional Science, Faculty of Medicine, Oeiras and Environmental Health Institute – ISAMB, Atlantica University, University of Lisbon, Lisbon, Portugal; [6]Nutrition division St Louis Hospital, Lisbon, Portugal; [7]Molecular Oncology Group, Portuguese Institute of Oncology, Porto Centre OPorto, Porto, Portugal; [8]Institute of Rocha Cabral, Lisbon, Portugal.

Introduction
Fat-free mass has a functional significance in aging. The objective of this study was to evaluate the prevalence of underweight in a Portuguese population of centenarians and their relationship with dehydration or sarcopenia.
Methods/design
Anthropometric data were obtained using standard procedures from 252 centenarians (100.26 ± 1.99 years), 77.8% women (W). Body composition was assessed by tetrapolar bioimpedance. It was considered dehydration: total body water (TBW) (%) < 45 (W) and < 50 male (M), and excess of fat mass (FM) (%): > 35 (W) and > 25 (M). The fat mass index (FMIndex): FM (kg)/height (m^2) and muscle mass index (MMIndex): MM (kg)/height (m^2) were calculated. Statistical methods: *T*-student, ANOVA, χ^2, linear correlation.
Results
In the sample, 61.4% had normal weight (BMI = 21.42 ± 1.86), but 25.3% were underweight (BMI = 16.84 ± 1.51), and of these, 28.8% were women. Instead, overweight (BMI = 27.52 ± 2.40) checked in 13.3% subjects, was predominant in men (10.6 vs 22.6%). Dehydration was observed in 12.9% of subjects and was tendentiously higher in women (15.4 vs 5.0%, $P = 0.087$). Excess of FM was found in 6.0% of subjects with no gender differences ($P = 0.225$). In the overweight subgroup there were differences in TBW ($P = 0.003$) and FM ($P = 0.022$) between genders, which was not observed in the underweight subgroup. The FMIndex in underweight or overweight subgroups did not vary significantly with gender. Muscle mass and MMIndex were different between genders, with the lowest values observed in underweight W compared to M (31.7 ± 3.96 vs 36.3 ± 2.84; $P = 0.01$) or to the other subgroups. There was a direct linear correlation between BMI and MM ($\beta(M) = 0.749$; $\beta(W) = 0.683$) and inverse with TBW ($\beta(M) = -0.428$; $\beta(W) = -0.397$), men and women, $P < 0.001$.
Conclusion
The underweight was more represented in the Portuguese centenarians. More than body water and FM, sarcopenia may be responsible for this low weight particularly in the women.

DOI: 10.1530/endoabs.37.EP113

EP114

Salt and puberty: self-regulated salt intake and the effect of salt on puberty

Dori Pitynski, Francis Flynn & Donal Skinner
University of Wyoming, Laramie, WY, USA.

The onset of puberty is changing in western countries. Puberty is the activation of the reproductive system, and is initiated by a complex series of events that are not fully understood. BMI has been linked to the advancement of puberty, but is unlikely to be the whole story as girls with a normal BMI are also advancing through puberty earlier. It is well known that western diets are high in calories, but the high salt content in these diets has been overlooked as a potential contributing factor. Salt consumption in the US and Europe far exceeds the recommended daily values. We hypothesize that salt intake may affect the timing of puberty. Our study on Sprague Dawley rats fed a high salt (8%) diet from weaning (Day 21) have a significant delay in the onset of puberty compared to a control, 0.3% salt, diet. Corticosterone levels were not different between control and high salt-fed rats, suggesting that the pubertal delay was not mediated by stress. FGF-21, which has been implicated in puberty onset, also did not differ between high salt and control rats. Salt intake was then varied to determine if lower salt intake may be stimulatory to puberty. Rats were fed no salt (0.01%), control (0.3%), 2%, or 4% salt. Rats fed no salt showed significantly delayed puberty. Our data showed a trend for 2% salt to cause a slight advancement in puberty, whereas 4% salt was not significantly different from control. To establish optimal salt-intake, rats were given the option of drinking saline (0.5% salt) or pure water while being fed no salt, 0.3%, or 2% salt in their chow. Rats fed no salt consumed 3.6 ± 0.8 mg/g rat per day salt compared to total food intake. Control rats consumed 2.9 ± 0.9 mg/g rat per day salt, and 2% salt fed rats consumed 5.1 ± 0.5 mg/g rat per day total salt. This data suggests that our 2 and 4% high salt diets are within the physiological ranges of salt consumption in rats. Our data shows that high salt can delay puberty at the highest levels, but may advance puberty at lower levels. Current salt loading in western populations has the potential to effect reproductive health, and warrants further attention.

DOI: 10.1530/endoabs.37.EP114

EP115

Exploring the psychosocial impact of congenital adrenal hyperplasia on children and their parents

Amy Simpson & Amy Hunter
Genetic Alliance UK, London, UK.

Congenital adrenal hyperplasia (CAH) is a genetic condition associated with a deficiency in cortisol and an overproduction of androgens, requiring life-long, daily medication. Little is known about the psychosocial impact of living with and treating CAH, particularly for the parents of young patients. The study was conducted by Genetic Alliance UK as part of the European Commission funded Treatment of Adrenal Insufficiency in Neonates (TAIN) Project, which aims to develop a new formulation of hydrocortisone for neonates and infants. Taking a qualitative approach, 17 semi-structured interviews were conducted in the UK with parents of children affected by CAH. Interviews were conducted face-to-face or via the telephone, and lasted approximately 1 h. They were audio-recorded, transcribed verbatim and analysed thematically with the support of Computer Assisted Qualitative Data Analysis Software, NVivo 8. As primary caregivers, parents experienced disruption to both their daily routine and sleep patterns as a result of their child's intensive medication regime. Parents reported a 'latent anxiety' associated with getting the right dose of medication at the right time, and often found separation from their child and delegating responsibility for treatment difficult. Parents expressed concerns about the potential impact of CAH on their child in the future and in particular, their child's ability to effectively self manage their condition. Challenges associated with the rarity of the condition also emerged during interviews including: a lack of awareness of CAH amongst the medical profession; delays in getting an accurate diagnosis; disparities in care across the UK; and difficulties finding the appropriate support. In conclusion, the study offers a rare insight in to the daily experiences of families affected by CAH and has important implications for the care and treatment of the condition in the future.

Disclosure
This work was supported by the Seventh Framework Programme (CORDIS FP7) of the European Commission, Health.

DOI: 10.1530/endoabs.37.EP115

EP116

Biochemical and molecular modelling analyses explain the functional loss of *HSD17B3* mutant G133R in three Tunisian patients

Roger Engeli[1], Bochra Ben Rhouma[2], Christoph R Sager[1], Faiza Fakhfakh[2], Leila Keskes[2], Angelo Vedani[1], Neila Belguith[2,3] & Alex Odermatt[1]
[1]University of Basel, Basel, Switzerland; [2]University of Sfax, Sfax, Tunisia; [3]Hedi Chaker Hospital, Sfax, Tunisia.

17β-Hydroxysteroid dehydrogenase type 3 (encoded by *HSD17B3*) catalyses the conversion of Δ4-androstene-3.17-dione to testosterone and has a key role in male sexual development. Mutations in the *HSD17B3* gene can result in reduced enzyme activity and decreased testosterone synthesis, leading to a rare autosomal recessive aetiology of 46, XY Disorders of Sex Development (46, XY DSD) named 17β-HSD3 deficiency. Here, we characterised three Tunisian patients from non-consanguineous families with a 46, XY karyotype and impaired virilisation of the external genitalia. The hormonal analysis and family history pointed to 17β-HSD3 deficiency. Genetic analysis revealed novel compound heterozygous mutations, i.e. a missense mutation (G133R) and a premature stop codon (C206X) in the *HSD17B3* gene. Using site-directed mutagenesis, an expression plasmid for 17β-HSD3 G133R was constructed. Additionally, expression plasmids for substitutions of glycine 133 to alanine (G133A), to phenylalanine (G133F), and to glutamine (G133Q) were created. WT and mutant enzymes were expressed in HEK-293 cells, followed by assessment of the conversion of radiolabeled Δ4-androstene-3.17-dione to testosterone. Mutants G133R, G133Q and G133F were almost completely inactive, whereas G133A retained more than 80% of WT activity. A homology model of 17β-HSD3 predicted that the loss of activity is due to a disruption of the cofactor-binding site. While an alanine at position 133 was still tolerated, more bulky side-chains led to steric hindrance thus preventing cofactor binding. The glycine at position 133 is highly conserved among the short-chain dehydrogenases. The functional analysis and homology modelling revealed an important role of this residue in the structural arrangement of the cofactor binding pocket. The results provide an improved mechanistic understanding of the 17β-HSD3 structure-function relationship and explained the 17β-HSD3 deficiency observed in the patients.

Disclosure
Swiss National Science Foundation 31003A_140961.

DOI: 10.1530/endoabs.37.EP116

EP117

Search for DHEASism and DHEASoma

Tomas Kurakovas[1], Ilona Banisauskaite[1], Birute Zilaitiene[1], Rytas Ostrauskas[1], Vaidotas Urbanavicius[2], Valentinas Matulevicius[1] & Irina Bilodid[3]
[1]Institute of Endocrinology, Lithuanian University of Health Sciences, Kaunas, Lithuania; [2]Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [3]University of Medicine, Minsk, Belarus.

Recently we described clinical case of 38-year-old fertile woman with sudden onset of a multiple clinical symptoms: weight gain, secondary amenorrhea, hirsutism and seizures. Adrenal tumour co-secreted high amounts of DHEA sulfate, testosterone (T) and aldosterone (A) (Matulevicius *et al*. 2014). The symptoms of the disease disappeared after laparoscopic removal of adrenal tumour, which proved to be an adrenocortical oncocytoma. A hypersecretion of A remained after resection of adrenal tumour, suggesting subclinical hyperandrosteronism. In attempt to find more such cases, we analysed results of DHEAS determinations in two university hospitals of Lithuania (Vilnius and Kaunas) during 1 year – 2014. We checked 1215 DHEAS results of 18–50-year-old woman to investigate our hypothesis. Increased DHEAS was considered when patient's DHEAS concentration was higher than maximal value of DHEAS indicated in the assay kit (11.76%) and was found in 143 cases. Mild increase was in 87.4%, moderate increase – in 9.8% and high increased – in 2.8%. These results confirm that mild increase of DHEAS is frequent (DHEASism). High increase of DHEAS is very rare – found only in four patients (DHEASoma). From these DHEASoma is confirmed in one patient and three are under investigation. Analysing the publications of the last 10-years about increased DHEAS concentration we found that increased DHEAS concentration is frequent in 18–50-year-old woman. These findings are linked to the polycystic ovary syndrome. In this syndrome DHEAS is increased in 20–30%. Elevated DHEAS was found in 9/11 adrenal cancers. Apart of our case, we found two more DHEASoma benign tumor cases in literature. Rarity of DHEASoma suggests that multicentral and multidisciplinary efforts are necessary for discovering and defining the disease.

DOI: 10.1530/endoabs.37.EP117

EP118

Psychological problems in children with diabetes mellitus type 1

Anzhalika Solntsava, Olga Zagrebaeva, Nadeya Peskavaya, Viktoryia Kozel & Hanna Mikhno
Belarusian State Medical University, Minsk, Belarus.

Objectives
The prevalence of diabetes mellitus type 1 (DM 1) had increased nowadays in children in Belarus. Psychological problems are one of side-effects of the disease.
Aim
To determine the presence of psychological problems in children with DM 1.
Methods
We examined 45 children (boys – 23, girls – 22) age 14.4 ± 0.8 years, with DM 1 in University hospital (Minsk) in 2014–2015 years. All children underwent psychological examination: depression self-rating scale (DSRS), child behaviour checklist (CBCL), quality of life questionnaire (QL). We examined: HbA1c, fasting glucose levels, day insulin (IU/kg), the experience of DM 1, stages on Tanner. Results were conducted using SPSS.18.
Results
The experience of DM 1 was 4.9 ± 3.6 years, HbA1c levels – 9.7 ± 1.7%, fasting glucose levels – 8.9 ± 1.5 mmol/l, insulin – 1.67 ± 0.3 IU/kg. ANOVA DSRS showed that sleep deprivation was dependent on the experience of DM 1 ($P=0.036$) and glucose level ($P=0.045$). Low concentration ($P=0.003$), mood ($P=0.001$), higher irritability ($P=0.017$), low emotional ($P=0.01$), low confidence ($P=0.044$) levels, pessimism ($P=0.027$) levels were dependent on the stage of Tanner. At the same time low mood was dependent on the glucose ($P=0.05$) and insulin (IU/kg) ($P=0.018$) levels; higher irritability – with the experience of DM 1 ($P=0$–04); low confidence with insulin (IU/kg) ($P=0.045$); weight increasing – with insulin (IU/kg) ($P=0.036$). CBCL and QL showed that disorganization ($P=0.02$), the loss of time due to DM 1 ($P=0.003$) and time, conducted on glucose monitoring ($P=0.005$) were correlated with the experience of DM 1. The higher experience of DM 1 the more children are afraid of teacher's attitude ($P=0.009$).
Conclusions
We found, that some psychological problems in children with DM 1 (sleep deprivation, low mood, low confidence) were dependent on the compensation of DM 1 and were increased due to puberty and the experience of DM 1.
DOI: 10.1530/endoabs.37.EP118

EP119

Influence of food on daily profiles of steroids
Michaela Duskova, Beáta Rácz, Monika Šrámková, Martin Hill & Luboslav Stárka
Institute of Endocrinology, Prague, Czech Republic.

Introduction
Whereas the daily profiles of the main steroid hormones are well known, minor differences in the course of their levels related to defined and standardised food intake were studied rarely.
Methods
Eight women (mean age 29.48 ± 2.99 years, mean BMI 21.3 ± 1.3 kg/m^2) in follicular phase of menstrual cycle were examined. The levels of C-peptide, glucose, LH, FSH, SHBG, cortisol, testosterone, dihydrotestosterone, progesterone, pregnenolone, oestrone and oestradiol were studied during a daily regimen (16 h) that included standardized food intake. The study protocol has been approved by Local Ethical Committee. A written informed consent was obtained from all participants.
Results
LH and FSH showed a monotonous decrease during the day with an implicated insignificant decrease after main meals. The course of androgen levels did not show much relation to food intake with the exception of dihydrotestosterone increase 2 h after lunch. SHBG evidently showed a small decrease after meals. C21 steroids showed a significant decrease 1 h after wakening up and then a monotonous decrease during the day. Cortisolemia continuously decreased during the day and an additional significant decrease of cortisol related to food intake was observed only 2 h after lunch. Estrogens did not show any striking trend of course during the day; oestradiol significantly decreased after lunch and dinner.
Conclusion
In our study the known nycthemeral rhythm of LH, FSH, cortisol, testosterone, progesterone and pregnenolone after food intake was confirmed but also significant changes after meals were observed in the levels of cortisol, estradiol and SHBG for the first time. The effect was seen only after the main meals (lunch and dinner). The effect of breakfast and snacks (small effect or long period from the meal and blood withdrawal) was probably hidden in the huge changes of the nycthemeral rhythm.
The study was supported by grants NT12340-5, NT11277-6, NT13890-4 IGAMZCR.
Disclosure
grants NT12340-5, NT11277-6, NT13890-4 IGAMZCR.
DOI: 10.1530/endoabs.37.EP119

EP120

Six-month interim safety and efficacy of different dose levels of transCon hGH administered once weekly versus standard daily human growth hormone replacement therapy in pre-pubertal children with growth hormone deficiency (GHD)
Pierre Chatelain[1], Oleg Malievsky[2], Klaudziya Radziuk[3], Heba Hassan Elsedfy[4], Evgenia Mikhailova[5] & Michael Beckert[6]
[1]University Claude Bernard, Lyon, France; [2]Bashkir State Medical University, Ufa, Russia; [3]2nd Children City Clinic, Minsk, Belarus; [4]Ain Shams University Hospital, Cairo, Egypt; [5]Samara State Medical University, Samara, Russia; [6]Ascendis Pharma A/S, on behalf of the TransCon hGH study group, Denmark.

Background
TransCon hGH is a long-acting prodrug of recombinant human GH (hGH) that releases into the blood compartment fully active unmodified hGH. TransCon hGH was shown in two Phase 1 studies and a Phase 2 study in AGHD to be safe and well tolerated and inducing an IGF-I pharmacodynamic response within the normal range throughout the dosing period. This interim analysis consists of 25 patients completing all 6 months of treatment.
Objectives
The objective of this study is to investigate i) safety and tolerability, ii) pharmacokinetics and pharmacodynamics, and iii) efficacy of TransCon hGH in children with GHD.
Design and methods
Pre-pubertal, treatment naïve GHD children received s.c. injections of one of three once-weekly TransCon hGH doses (0.14, 0.21 or 0.30 mg hGH/kg per week) or daily hGH (Genotropin; 0.03 mg hGH/kg per day = 0.21 mg/kg per week) over a 6-month treatment period.
Results
Mean annualised height velocities ranged from 11.9 cm for the 0.14 mg/kg per week dose to 14.5 cm for the 0.30 mg/kg per week dose, which were comparable to 11.5 cm for the active comparator, Genotropin at a 0.21 mg/kg per week dose. No SAEs occurred and injection site reactions were generally mild and transient and occurred in only a few patients. Maximum hGH blood concentrations are comparable between equivalent weekly doses of TransCon hGH and daily hGH; and a dose–proportional increase in IGF-I levels into the normal range was observed for the three TransCon hGH dose levels.
Conclusions
To date, TransCon hGH has demonstrated efficacy and safety comparable to that observed with daily hGH. Injection site reactions have been mild and similar to what is expected with daily hGH injections, with no nodule formation or lipoatrophy noted. This TransCon hGH Phase 2 study conducted in a paediatric population confirms the excellent safety and efficacy profile observed in previous clinical trials.
Disclosure
This study was sponsored by Ascendis Pharma A/S.
DOI: 10.1530/endoabs.37.EP120

EP121

Analysis of androgen profile in teenage girls and young women with acne of various severity
Elzbieta Sowinska-Przepiera[1], Elzbieta Andrysiak-Mamos[1], Aleksandra Walkowiak[1], Mirela Niedzielska[1], Grazyna Jarzabek-Bielecka[2], Witold Kedzia[2] & Anhelli Syrenicz[1]
[1]Department of Endocrinology, Metabolic Diseases and Internal Diseases, Pomeranian Medical University, Szczecin, Poland; [2]Department of Gynaecology, Poznan University of Medical Sciences, Poznan, Poland.

Introduction
Acne is the most commonly diagnosed skin condition in teenage girls and young women. Acne results from androgen excess or hypersensitivity of the skin to normal androgen levels. Therefore, determination of androgen concentrations in patients with acne may facilitate early implementation of appropriate treatment. The aim of the study was to retrospectively analyse the profiles of androgen concentration in female patients with acne of various severity.
Material and methods
The study included 270 girls and young women (16–25 years of age) with acne. The participants were classified based on the severity of acne assessed according to the Leeds grading system: group I – mild acne ($n=80$), group II – moderate acne ($n=90$), group III – severe acne ($n=20$), and group C – controls ($n=80$). Concentrations of androgens: DHEAS, androstenedione, testosterone, and sex hormone binding globulin (SHBG) were determined in all the study participants, and the level of bioavailable testosterone (BAT) was calculated.

Results
Patients from the investigational groups I, II, and III presented with significantly higher concentrations of androgens: DHEAS ($P<0.000$), testosterone ($P<0.000$), androstenedione ($P=0.007$), and BAT ($P<0.000$) than the controls. Moreover, we found significant inverse correlations between the concentrations of testosterone and androstenedione ($r=-0.420$, $P<0.000$), SHBG and DHEAS ($r=-0.391$, $P<0.000$), SHBG and androstenedione ($r=-0.272$, $P<0.009$) in group II and III participants.
Conclusions
Determination of the hormonal profile of girls with acne is vital for the management of this condition and prevention of its recurrence. Juvenile acne is a clinical marker of hyperandrogenism and can be considered a transient manifestation of puberty in teenage girls.

DOI: 10.1530/endoabs.37.EP121

EP122

The NCEP ATP III criteria may overestimate the diagnosis of metabolic syndrome in obese and overweight adolescents

Hasan Sav[1], Umut Mousa[1], Osman Koseoglulari[1] & Ruveyde Bundak[2]
[1]Department of Endocrinology and Metabolism, B Nalbantoglu Hospital, Nicosia, Cyprus; [2]Department of Pediatric Endocrinology, Istanbul Univeristy, Istanbul, Turkey.

Introduction
The diagnosis of the metabolic syndrome is less definite in children and adolescents compared to adults. The International Diabetes Federation (IDF) and National Cholesterol Education Program Adult Treatment III guidelines (NCEP ATP III) have proposed two different criteria for its diagnosis in these age groups. In this study we planned to compare these two criterias in detecting the metabolic syndrome in obese and overweight adolescents in a study group in Northern Cyprus.
Subjects and methods
A total of 274 obese and 46 overweight adolescents were included from the northern region of Cyprus. The mean age was 13.72 ± 1.15 years (11.2–17). 156 (48.8%) were girls and 164 were boys (51.2%). We measured the subjects' blood pressure, fasting blood glucose levels, HDL-C levels, triglycerides, body weight to the nearest 0.1 kg, body height to the nearest 0.1 cm. We calculated the BMI by dividing the weight in kilograms to the height in centimetres squared.
Results
Metabolic syndrome was detected in 18.2 and 47.8% in obese adolescents and 17.4 and 30.4% in overweight adolescents according to the IDF and NCEP ATP III criteria respectively.
Conclusion
The prevalence of metabolic syndrome was much higher when using the NCEP-III criteria compared to the IDF criteria both in obese and in overweight adolescents leading to a debate in determining which criteria to be used.

DOI: 10.1530/endoabs.37.EP122

EP123

Is there a link between lipid profile and thyroid function modification during somatropinum treatment for GH deficiency in children?

Lavinia Stejereanu[1], Luminita Cima[1], Alice Albu[1,2], Carmen Barbu[1,2] & Simona Fica[1,2]
[1]Elias Emergency Hospital, Bucharest, Romania; [2]UMF Carol Davila, Bucharest, Romania.

Background
Previous studies suggested that treatment with somatropinum in children with GH deficiency (GHD) may alter lipid profile and pituitary–thyroid axis function. However, results are divergent and data regarding a possible association between changes of thyroid function and of circulating lipids are scarce. The aim of this study was to report the changes of the lipid profile in children with GHD treated with somatropinum and the relationship between thyroid function and circulating lipids modifications.
Patients and methods
We performed a retrospective study in which we included children diagnosed with GHD ($n=101$, 68 males and 33 females with a mean age of 8.6 years) treated with somatropinum during January 2008–January 2012. We recorded from the medical files the following data: weight, height, total-, HDL-, LDL-cholesterol, triglycerides, TSH, and free T_4 at inclusion (start of the treatment) and every 6 months during the first year of treatment with somatropinum.
Results
Patients with GHD had increased serum triglycerides levels at 6 months after initiation of treatment (from a mean of 60.41 mg/dl at inclusion to 79.93 mg/dl, $P=0.025$), increased HDL (from a mean 55.35 mg/dl at inclusion to 60.50 mg/dl, $P=0.05$) and decreased LDL after 1 year (from a mean of 99.35 to 88.35 mg/dl, $P=0.05$) Although, TSH and free T_4 decreased at 6 and 12 months in comparison with baseline, this modification was not statistically significant. However, the changes in triglycerides and LDL levels were significantly correlated with the TSH levels modification from baseline ($r=0.549$, $P=0.015$ for triglycerides and $r=0.731$, $P=0.011$ for LDL).
Conclusion
Our study showed that lipid profile significantly changes during treatment with somatropinum for GHD in children and this alteration could be partially due to a slight modification of thyroid function. However, further prospective studies are necessary to clarify this aspect.

DOI: 10.1530/endoabs.37.EP123

EP124

Haploinsufficiency of the *SHOX* gene associated with mosaicism 45,X/46,XY with chromosome Y ring as causes of delayed growth and puberty

Diana Martins[1], Carla Baptista[1], Margarida Bastos[1], Ana Garabal[2], Joaquim Sá[1], Carolina Moreno[1], Daniela Guelho[1], Nuno Vicente[1], Luís Cardoso[1], Margarida Balsa[3], Diana Oliveira[1] & Francisco Carrilho[1]
[1]Endocrinology, Diabetes and Metabolism Department, Coimbra Hospital and University Centre, Coimbra, Portugal; [2]Genetics Department, Pediatric Hospital Carmona da Mota of Coimbra Hospital and University Centre, Coimbra, Portugal; [3]Endocrinology, Diabetes and Nutrition Department, Baixo Vouga Hospital Centre, Aveiro, Puerto Rico, Portugal.

Introduction
The height growth is regulated by multiple factors, including specific genetic mutations that ensure correct differentiation and proliferation of chondrocytes. We present a case of double association of haploinsufficiency of the *SHOX* gene with a mosaic 45,X/46,X,r(*Y*) karyotype responsible for growth and pubertal delay.
Case
Male patient, observed in endocrinology consultation at age of 12, with constitutional delay of growth (below the 5th percentile) and pubertal delay. Hormonal analytical study excluded GH deficit and showed reduction of total testosterone (0.2 ng/ml) and free testosterone (0.2 pg/ml) and proof of GnRH with abnormal response. Coeliac disease was excluded. Radiographic study presented delay of skeletal maturation and echographic study established the presence of well positioned testes with normal morphology. Magnetic resonance of the pituitary was also normal. Karyotype's study was performed and revealed the presence of a mosaic 45,X/46,XY. About 63% of the cells didn't had the *SRY* gene.
He made two cycles of 4 months with testosterone enanthate (dose of 62.5 mg/month) with regular progression of pubertal development, however the patient kept growth delay in the follow up. Now, at the age of 18, it was performed karyotype study with extended banding that confirmed an aneuploid line for the Y chromosome (45,X) without *SRY* gene, and a line with a ring Y chromosome (46,X,r (Y)) without the *SHOX* gene and the presence of *SRY*.
Conclusions
The case described highlights the importance of accurate diagnosis of sex chromosome abnormalities and mutations of the *SHOX* gene to establish a diagnostic strategy and appropriate therapy in patients with constitutional delay of growth and puberty. We also recommend for the need of regular monitoring, because the potentially associated complications.

DOI: 10.1530/endoabs.37.EP124

EP125

Endocrine and metabolic profiles in adults with Prader–Willi syndrome

Delia Bogdanet, Agnieszka Pazderska, Mark Sherlock & James Gibney
The Adelaide and Meath Hospital, Dublin Incorporating the National Children's Hospital, Dublin, Ireland.

Introduction
Prader–Willi syndrome (PWS) is a genetic syndrome usually diagnosed in childhood. Its reported prevalence ranges from one in 8000 to one in 45 000 with geographical variation. Clinical manifestations include obesity, hyperphagia, short stature, incomplete sexual development, and cognitive disabilities. The majority of published data regarding PWS comes from paediatric populations.
Materials and methods
This is a retrospective observational study of adult patients with PWS performed in an Irish tertiary referral centre. We collected anthropometric measurements, hormonal data, results of genetic testing, and clinical data regarding co-morbid conditions, psychological, and social circumstances.
Results
Twenty-two adult patients (15 women) with a diagnosis of PWS were identified. The median age was 24.5 years. Median height and BMI was 154.3 cm and 41.7 kg/m^2 respectively. Eighteen of patients were assessed for GH deficiency (GHD), 15 using the insulin tolerance test. Sixteen (88.2% of the patients tested) had severe GHD. Fifteen received GH therapy. Height velocity was 4 cm in the first 6 months and 9 cm in the first year of therapy. Fifty percent of patients had evidence of obstructive sleep apnoea; 90.9% had spinal scoliosis; 81.8% had hypogonadism; and 50% of those who had a DXA scan had osteoporosis ($n=5$). Fifty percent of patients had abnormal blood pressure, 22% had lipid abnormalities and 13% had an abnormal HbA1c. 21/22 had learning disabilities, and 50% had associated psychiatric diagnoses. There was no difference in BMI, height, lipids, fasting glucose between GH treated and untreated patients. However the number of patients was small so this could be underpowered to detect a true difference.
Conclusion
Adult patients with PWS have multiple endocrine abnormalities and require careful follow up and management. Early diagnosis and management of endocrine manifestations will potentially improve health and developmental outcomes in adulthood.

DOI: 10.1530/endoabs.37.EP125

EP126

Diagnostic value of amino-terminal peptide of type I procollagen when retesting GH deficiency in the transition period

Mariana Costache-Outas[1,2], Camelia Procopiuc[2], Andra Caragheorgheopol[2], Raluca Costache[3] & Simona Fica[1,4]
[1]'Carol Davila' University of Medicine and Pharmacy, Bucharest, Romania; [2]National Institute of Endocrinology 'C.I.Parhon', Bucharest, Romania; [3]Clinical Hospital Dr. Ioan Cantacuzino, Bucharest, Romania; [4]Elias Emergency University Hospital, Bucharest, Romania.

N-terminal peptide of type I procollagen (P1NP) is a marker of GH (hGH) anabolic action on bone formation. We evaluated the diagnostic value of P1NP in GH deficiency (GHD) in the transition period using receiver operating characteristic (ROC) plot analysis. We compared the diagnostic value of P1NP with IGF1. 16 male patients (chronological age, 16.6–21.5) with GH replacement therapy during childhood (ten IGHD and six MPHD) were evaluated at minimum 3 months after completion of treatment (1.86 ± 1.46 years from rhGH withdrawal). A control group (CG) of nine healthy males (chronological age, 15.2–17.5) was selected. GH secretion was evaluated in IGHD group using insulin tolerance test and were divided as persistent IGHD (three patients) or reversible IGHD (seven patients) according to a GH cut-off below or above 5.6 ng/ml. There were no significant difference between IGF1 and P1NP in the control group and reversible IGHD group. The SDS for IGF1 and P1NP was calculated from the 16 participants with normal GH status (controls and reversible IGHD). The ROC plot showed that the best IGF1 SDS cut-off line was -0.76 (sensitivity (S), 87.5%; specificity (Sp), 88.9%, AUC$=0.944$). For P1NP SDS, the best cut-off line was -0.81 (sensitivity (S), 81.3%; specificity (Sp), 66.7%, AUC$=0.743$).
Conclusion
IGF1 is a better GH biomarker for diagnostic of persistent growth deficiency in the transition period with better specificity and sensibility comparing to P1NP.
Disclosure
This work was supported by the Educational Grant SOP HRD (POSDRU)/159/1.5/S/135760, 2014.

DOI: 10.1530/endoabs.37.EP126

EP127

Precocious puberty in the obese child as a diagnostic challenge

Pawel Matusik, Zofia Prokopowicz & Ewa Malecka-Tendera
Department of Paediatrics, Paediatric Endocrinology and Diabetes, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland.

The aim of this study was to evaluate whether the coexistence of obesity in children with precocious puberty symptoms influences significantly the diagnostic process.
Material and methods
We retrospectively analysed a group of 200 children's records (F/M 164/36) hospitalised because of precocious puberty suspicion. The analysis evaluated the nutritional status based on BMI percentile level, compatibility between the bone age and the chronological age; and the final clinical diagnosis.
Results
In the analysed group excessive body weight was found in 66 (33%) children – overweight in 34 (17%) and obesity in 32 (16%) patients respectively. It is noticeable that children with excessive body weight are significantly more likely to have mild variants of precocious puberty (71% vs 66.4%) despite the fact that the accelerated bone age in this group was more frequently observed (47% vs 24.6%). In the group with mild variant of PP and accelerated bone age ($n=41$ (28.9%)) up to 75.6% of children were overweight or obese. In the group of CPP accelerated BA was observed only in 23 (52.3%) children. Frequently recognized variant of PP in obese children was premature pubarche ($n=20$ (62.5%)).
Conclusions
Obesity and overweight significantly modifies puberty, and by accelerating the bone age can hinder the initial diagnosis of PP. The bone age acceleration seems to be poor indicator of central precocious puberty, especially in obese children. The population of overweight and obese children is dominated by a mild variant of precocious puberty – premature pubarche.

DOI: 10.1530/endoabs.37.EP127

EP128

Is thyroid function related to masked hypertension?

Ihsan Ates[1], Mustafa Altay[1], Mustafa Kaplan[1], Nihal Ozkayar[2], Erdem Alagüney[1] & Adem Ozkayar[3,4]
[1]Department of Internal Medicine, Ankara Numune Education and Research Hospital, Ankara, Turkey; [2]Department of Nephrology, Ankara Numune Education and Research Hospital, Ankara, Turkey; [3]Department of Family Medicine, Ankara Numune Education and Research Hospital, Ankara, Turkey; [4]Department of Family Medicine, Faculty of Medicine, Hitit University, Çorum, Turkey.

Background
Thyroid hormones affect almost all the tissues of the body and their cardiovascular effects are very significant. The relationship between masked hypertension (MHT) and thyroid hormones is not known. Therefore, we sought to investigate any relationship between patients with MHT, newly diagnosed by home blood pressure monitoring, and thyroid hormones.
Methods
Patients older than 18 years of age without a previous diagnosis of hypertension and presenting to the Outpatient Department with hypertensive symptoms were enrolled. Patients were categorized into three groups as MHT, primary hypertension (PHT) and normotensive, according to blood pressures taken at home and office. The levels of TSH, free triiodothyronine (fT_3), and free thyroxine (fT_4) were measured by electro-chemiluminescence immunoassay in the three groups.
Results
Of the 712 participants enrolled in the study, 206 had PHT, 73 had MHT, and 433 were normotensive. The average log(TSH) level was higher while average fT_4 level was lower in the PHT group as compared to the MHT and normotensive groups. Log(TSH) and fT_4 levels were similar in the MHT and normotensive groups. Stepwise multiple regression analysis showed average systolic and diastolic blood pressures to be related to log(TSH), fT_4, and presence of hypothyroidism in the PHT group. No such relationship was found in the MHT and normotensive groups.
Conclusion
In conclusion, no relationship was found with thyroid hormones in patients with MHT in contrast to patients with PHT. Randomised controlled studies with a larger population size and longer follow-up duration are needed to understand the relationship between blood pressure values and thyroid hormones in patients with MHT.

DOI: 10.1530/endoabs.37.EP128

EP129

Effect of metformin on sex steroid levels in postmenopausal type 2 diabetic patients

Ugur Ünlütürk[1], Filiz Bakar[2], Yuksel Ürün[1], Serpil Nebioglu[2] & Ali Riza Uysal[1]
[1]Faculty of Medicine, Ankara University, Ankara, Turkey; [2]Faculty of Pharmacy, Ankara University, Ankara, Turkey.

Introduction
Metformin treatment was associated with decreased risk of various cancers including breast cancer. Exposure to sex steroid is related with increased risk of breast cancer. In this study, we aimed to evaluate the effect of metformin treatment on serum levels of sex steroids and sex hormone binding globulin (SHBG) in postmenopausal women with type 2 diabetes mellitus.
Methods
Postmenopausal patients with newly diagnosed type 2 diabetes were recruited to the study. Before starting life-style modifications and metformin treatment anthropometric measurements were done and fasting blood samples were collected in order to evaluate insulin, glucose, HbA1c, serum levels of sex hormones, and SHBG. All of the basal tests were repeated for each subject at the end of 12 weeks.
Results
At the end of 12 weeks, 36 patients completed the study and were included into analyses. Five of 36 patients did not use metformin due to gastrointestinal side effects or noncompliance with therapy. Remaining patients used at least 500 mg to maximum 2000 mg/day of metformin treatment. Mean body-weight and body fat mass, fasting insulin, HbA1c levels significantly decreased in patients who used metformin. Patients receiving metformin treatment also showed significant decrease in testosterone (−28%), oestradiol (−9%), and oestrone levels (−11.5%), and significant increase in DHEAS (8.9%) and SHBG (4.5%) levels. A borderline significant decrease was seen in androstenedione levels as well. Fasting plasma glucose and oestrone sulphate levels did not change significantly. When compared to the patients who did not use metformin therapy, changes in oestradiol levels were significant, and changes in estrone and testosterone levels marginally significant in patients receiving metformin.
Conclusion
Metformin treatment may have favourable effect on breast cancer risk through decreasing androgen and oestrogen levels in postmenopausal type 2 diabetic patients.

DOI: 10.1530/endoabs.37.EP129

EP130

Serum prolactin levels in transgender persons before and during cross-sex hormonal treatment

Nienke Nota, Maartje Klaver, Martin den Heijer, Marieke Dekker & Annemieke Heijboer
VU University Medical Center, Amsterdam, The Netherlands.

Introduction
Gender dysphoria refers to the incongruence between the subject's experienced sex on the one hand and the assigned sex on the other hand. Several studies assume a relationship between oestrogen substitution therapy and serum prolactin levels.
Aim
The aim of this study is to get more insight into the effect and time-course of changes in serum prolactin levels during cross-sex hormone therapy.
Methods
This prospective study included 82 transgender persons who completed 1 year of treatment, 45 male-to-female individuals (MtF's) (mean age ± s.d. 34 ± 13 years) and 37 female-to-male individuals (FtM's) (mean age ± s.d. 27 ± 10 years). MtF's were treated with cyproteronacetate (50 mg/day) and estradiol valerate (2–4 mg/day) or an estradiol patch (200 μg/week). FtM's were treated with testosterone esters i.m. (250 mg/2 weeks), testosterone undecanoate i.m. (1000 mg/12 weeks), or testosterone gel (50 mg/day). We determined serum prolactin levels at baseline and after 3 and 12 months. Serum prolactin was measured by immunometric assay (Centaur, Siemens).
Results
In MtF's mean serum prolactin levels increased from 0.16 to 0.41 U/l (160% (132–188%)) between 0 and 3 months and from 0.41 to 0.47 U/l (15% (0.2–29%)) between 3 and 12 months (mean level in biological women 0.28 U/l). In FtM's mean serum prolactin levels decreased from 0.27 to 0.23 U/l (−16% (−28 to −4%)) between 0 and 3 months and from 0.23 to 0.21 U/l (−9% (−30 to 13%)) between 3 and 12 months (mean level in biological men 0.16 U/l).
Conclusions
In MtF's an increase in mean serum prolactin levels was seen whereby those levels exceeded mean serum prolactin levels of biological women. In FtMs a decrease in mean serum prolactin levels was seen whereby those levels did not reach the values of biological men. In both groups the biggest change was observed during the first 3 months of treatment.

DOI: 10.1530/endoabs.37.EP130

Reproduction, endocrine disruptors and signalling

EP131

25-Hydroxyvitamin D status in elderly patients with Hashimoto's thyroiditis

Fulden Sarac[1], Sumru Savas[1], Pelin Tütüncüoglu[2] & Fehmi Akcicek[1]
[1]Department of Geriatrics Medicine, Izmir, Turkey; [2]Department of Endocrinology, Katip Celebi University, Atatürk Training and Research Hospital, Izmir, Turkey.

Introduction
Low serum levels of 25-hydroxyvitamin D (25(OH)D3) lower than has been reported to be prevalent in several autoimmune diseases. The aims of the study were i) to evaluate the 25(OH)D3 levels in patients with Hashimato's thyroiditis (HT) and ii) to investigate the relationships between 25(OH)D3, TSH, free T_4, free T_3, and anti-thyroid peroxidase (anti-TPO) levels in elderly patients with HT.
Subjects and method
Study population included 80 (mean age 58.1 ± 9.3 years; 60 females and 20 males) patients with HT. Data such as 25(OH)D3, TSH, fT_4, fT_3, and anti-TPO tests were retrospectively searched. Vitamin D insufficiency was defined as 25(OH)D3 concentrations lower than 30 ng/ml.
Results
In elderly with HT, mean levels of 25(OH)D3 were found to be 39.7 ± 6.5 ng/ml. However, mean levels of 25(OH)D3 were 52.0 ± 12.3 ng/ml in patients with HT (age <60 years) ($P=0.05$). In patients with HT (age <60 years) means level of 25(OH)D3 concentrations were inversely correlated with the anti-TPO levels ($r=-0.700$, $P=0.04$). And also, in elderly group, mean levels of 25(OH)D3 concentrations were positively correlated with the fT_4 levels ($r=-0.700$, $P=0.04$).
Conclusion
25(OH)D3 deficiency was significantly higher in elderly. And also, mean levels of 25(OH)D3 were positively correlated with fT_4 in elderly with HT, but inversely correlated with anti-TPO levels in patients with HT (age <60 years).

DOI: 10.1530/endoabs.37.EP131

EP132

How much insulin resistance in polycystic ovary syndrome: comparison of HOMA and insulin resistance (Belfiore) index models

Krzysztof Lewandowski, Katarzyna Lukasiak, Katarzyna Marczuk, Aleksandra Dukowicz, Magdalena Cedro, Malgorzata Bienkiewicz, Elzbieta Skowronska-Jozwiak & Andrzej Lewinski
Department of Endocrinology and Metabolic Diseases, The Medical University of Lodz, Lodz, Poland.

Background
Polycystic ovary syndrome (PCOS), the commonest endocrinopathy of women in the reproductive age is often accompanied by insulin resistance (IR). The aim of the study was to assess the prevalence of IR in women diagnosed with PCOS, where IR was assessed by methods most commonly used in clinical practice, i.e. homeostatic model assessment (HOMA) and insulin resistance index (IRI), also known as the Belfiore index.
Patients and methods
The study involved 137 women diagnosed with PCOS according to the Rotterdam (2003) criteria, age (mean ± s.d.) 25 ± 7 years, BMI 27.61 ± 7.43 kg/m^2. IR was assessed according to the HOMA method (glucose (mmol/l)) × (insulin (μU/ml))/22.5 and IRI methods, where IRI, can be obtained through the formula: $2/((1/(INSp \times GLYp))+1)$, where where INSp, GLYp = insulinemic and glycemic, areas during 75 g OGTT. IR was diagnosed for IRI >1.25.
Results
There was a strongly significant ($P<0.0001$), but still relatively moderate correlation between IRI and HOMA methods ($r=0.5$ and $r=0.57$ for a linear and non-linear model respectively). IR was much more prevalent according to IRI (49.6%) than according to HOMA (22.6 and 15.8% for 3.46 and 3.8 cut-off points,

respectively, $P<0.01$). The majority of patients with high HOMA also had high IRI (e.g. 86% for HOMA >3.8), but the majority of patients with raised IRI, would not be diagnosed as insulin resistant according to HOMA (61.7 and 73.5%, for $HOMA_{3.46}$ and $HOMA_{3.80}$ respectively). IRI concentrations were higher among patients with concomitantly raised HOMA (1.55 ± 0.18 vs 1.44 ± 0.14, $P=0.014$ and 1.60 ± 0.18 vs 1.44 ± 0.13, $P=0.0008$ for $HOMA_{3.46}$ and $HOMA_{3.80}$ respectively).

Conclusions

IRI, based on glucose and insulin measurements during OGTT demonstrates more cases of insulin resistance than HOMA model in women with PCOS. Therefore, detection of insulin resistance among women with PCOS is highly method-dependent with more severe cases being detected with HOMA than with IRI.

DOI: 10.1530/endoabs.37.EP132

EP133

Surrogate markers of insulin resistance obtained from oral glucose tolerance test in different phenotypes of polycystic ovary syndrome

Ivana Bozic Antic[1], Jelica Bjekic-Macut[2], Danijela Vojnovic Milutinovic[3], Dusan Ilic[1], Bojana Popovic[1], Tamara Bogavac[1], Biljana Kastratovic-Kotlica[4], Tatjana Isailovic[1], Valentina Elezovic[1], Sanja Ognjanovic[1], Svetozar Damjanovic[1] & Djuro Macut[1]

[1]Clinic of Endocrinology, Diabetes and Metabolic Diseases, Faculty of Medicine, University of Belgrade, Belgrade, Serbia; [2]CHC Bezanijska kosa, Belgrade, Serbia; [3]IBISS, University of Belgrade, Belgrade, Serbia; [4]Clinic of Gynecology and Obstetrics, Faculty of Medicine, University of Belgrade, Belgrade, Serbia.

Introduction

Insulin resistance (IR) is a well recognised feature in women with polycystic ovary syndrome (PCOS). The aim of this study was to analyse IR indices obtained from oral glucose tolerance test (OGTT), in different PCOS phenotypes.

Methods

We evaluated 240 PCOS women (PCOS: 24.86 ± 5.97 kg/m^2; 25.25 ± 4.98 years) diagnosed using ESHRE/ASRM criteria and 70 BMI-matched healthy women (controls: 26.14 ± 4.86 kg/m^2; 30.76 ± 5.82 years). PCOS group was divided into four phenotypes: A (anovulation (ANOV), hyperandrogenism (HA), and polycystic ovary morphology (PCOM)), B (ANOV and HA), C (HA and PCOM), and D (ANOV and PCOM). Phenotype D had lower BMI in comparison to all other phenotypes ($P<0.05$). Standard OGTT with 75 g glucose was performed in all subjects. IR was estimated by the homeostasis model assessment of IR (HOMA-IR), insulin sensitivity index (ISI), hepatic IR index (HIRI), and insulinogenic index (IGI). Areas under insulin (AUCi) and glucose (AUCg) and their ratio, termed the insulin secretion-sensitivity index-2 (ISSI-2) were calculated.

Results

The whole PCOS group in comparison with controls had higher levels of basal glucose (4.89 ± 0.45 mmol/l vs 4.57 ± 0.50 mmol/l, $P=0.003$) and insulin (17.16 ± 10.36 mU/l vs 11.95 ± 6.53 mU/l, $P<0.001$), HOMA-IR (3.64 ± 2.38 vs 2.66 ± 1.48, $P<0.001$), HIRI (3.98 ± 2.65 vs $2.20\pm0.85\times10^6$, $P=0.027$), IGI (22.13 ± 15.86 vs 10.31 ± 4.13, $P=0.027$), AUCg (711.63 ± 153.87 vs 670.68 ± 86.48, $P=0.012$), AUCi (7847.97 ± 4660.48 vs 4647.80 ± 1665.78, $P=0.029$), and ISSI-2 (10.83 ± 5.49 vs 6.51 ± 2.14, $P=0.019$) while ISI (4.50 ± 2.14 vs 6.04 ± 2.71, $P=0.032$) was lower. Phenotype B had higher levels of basal insulin and HOMA-IR then phenotypes A, C, and D while AUCi, HIRI, ISSI-2 were higher and ISI was lower then in phenotypes C and D. There were no differences in basal glucose, AUCg and IGI between phenotypes.

Conclusion

In our group of women with PCOS, classical hyperandrogenemic phenotype B was characterised with the most exaggerated indices of IR.

DOI: 10.1530/endoabs.37.EP133

EP134

A case of dyskeratosis congenita associated with hypothyroidism and hypogonadism

Nilufer Ozdemir Kutbay[1], Zehra Erdemir[2], Banu Sarer Yurekli[1], Emin Karaca[3], Mehmet Erdogan[1], Sevki Cetinkalp[1], Gulsen Kandiloglu[4], Gokhan Ozgen[1], Ferda Ozkinay[3] & Fusun Saygili[1]

[1]Endocrinolgy and Metabolism Department, Faculty of Medicine, Ege University, Izmir, Turkey; [2]Internal Medicine Department, Faculty of Medicine, Ege University, Izmir, Turkey; [3]Genetics Department, Faculty of Medicine, Ege University, Izmir, Turkey; [4]Pathology Department, Faculty of Medicine, Ege University, Izmir, Turkey.

Introduction

Dyskeratosis congenita is a rare multisystemic disease characterised with atrophy on skin, pigmentation, nail dystrophy, leukoplakia in mucous membrane, bone marrow failure, and tendency to malignancy. We present a rare case of dyskeratosis congenita associated with hypothyroidism and hypogonadism.

Case

A 30-year-old male patient was referred to Endocrinology Department with the findings of micropenis and atrophic testicles. His parents had cousin marriage. Physical examination results: BP: 130/80 mmHg, height: 172 cm, weight: 83 kg, and BMI: 28 kg/m^2. There were hypopigmented skin lesions in the whole body. The skin was dry and the nails were dystrophic. His axillary and pubic hair was normal but facial hair was scarce. He had alopecia in 1/3 of outer eyebrow (Omnibus sign) and saddle nose. Micropenis and testicles were found to be atrophic. The laboratory findings: WBC: 3140/mm^3, neutrophil: 1740/mm^3, Hb: 12.5 g/dl, plt: 187 000/mm^3, free testosterone: 1.4 pg/ml, total testosterone: 0.70 ng/ml, FSH: 77.28 mIU/l, LH: 15.38 mIU/l, E_2: <20 pg/ml, prolactin: 6.77 ng/ml, DHEAS: 222.1 µg/dl, free T_3: 3.35 pg/ml, free T_4: 0.98 ng/dl, TSH: 10.88 mIU/l, anti-TG: 203 IU/ml, ACTH: 24.1 pg/ml, and cortisol: 13.34 µg/dl. Hypergonadotropic hypogonadism was suspected as testosterone was low and FSH and LH were high. Hyperkeratosis keratoderma was found in skin biopsy. In the biopsy of lymph node from right cervical, we found disseminated histiocytic proliferation that changes the normal appearance of lymph node and granulomas that are characterised with rare giant cell formation and that don't include necrosis.

Conclusion

Dyskeratosis congenita is a rare disease showing X-linked recessive inheritance along with autosomal dominant and recessive forms. Although the pathogenesis of the disease is still unknown, *DKC1* gene localised to Xq28 is thought to be responsible for the X-linked dyskeratosis congenita. Our patient is still genetically studied. In this syndrome, the association of hypothyroidism and hypogonadism should be kept in mind.

DOI: 10.1530/endoabs.37.EP134

EP135

NMDA receptor mediated limbic encephalitis in a woman with mature cystic ovarian teratoma: a case report

Melinda Vanya[1], Zoltan Kovacs[2,4], Nikos Gorgoraptis[3], Afram Salek-Haddadi[3], Laszlo Kovacs[4] & Gyorgy Bartfai[1]

[1]Department of Obstetrics and Gynaecology, Faculty of Medicine, Albert Szent-Györgyi Health Centre, University of Szeged, Szeged, Hungary; [2]Department of Psychiatry, Faculty of General Medicine, Albert Szent-Györgyi Health Centre, University of Szeged, Szeged, Hungary; [3]Department of Neurology, Centre for Neurosciences, The Royal London Hospital, London, UK; [4]Department of Rheumatology, Faculty of General Medicine, Albert Szent-Györgyi Health Centre, University of Szeged, Szeged, Hungary.

Objective

Our aim was to present a case of paraneoplastic NMDA-R antibody-mediated limbic encephalitis in a woman with OT thereby providing information facilitating diagnosis of OT in women, who present with symptoms of paraneoplastic limbic encephalitis (LE) for obstetricians and gynaecologists with appropriate.

Case

We report the case of a 25-year-old women, who developed NMDA-R-antibody mediated autoimmune encephalitis and who displayed confusion, disorientation, a behavioural disturbance with agitation and features of paranoia and at least one reported generalised tonic clonic seizure associated with orofacial dyskinesia. Magnetic resonance imaging revealed 3.3 cm functional ovarian cyst measuring which was removed surgically and demonstrated histologically to be a mature cystic OT. The serum was positive for antibodies to NMDA receptors. Following i.v. immunoglobulin treatment, oophorectomy and a 5-day course of plasma exchange, followed by corticosteroid and azathioprine immunosuppressive therapy, the patient displayed a significant clinical improvement.

Conclusion

Cystic teratomas are common benign ovarian lesions in women of reproductive age. Although the association of OTs and NMDA-R antibody-mediated encephalitis has been described in the neurologic literature, this relationship needs to be considered from on interdisciplinary aspect by the healthcare providers.

DOI: 10.1530/endoabs.37.EP135

EP136

The impact of bleeding patterns and hormonal contraceptives on migraine headache: a retrospective cross-sectional study

Melinda Vanya[1], Ivan Devosa[3], Fanni Bokros[2], Marta Szucs[1], Delia Szok[2] & Gyorgy Bartfai[1]
[1]Department of Obstetrics and Gynaecology, Albert Szent-Gyorgyi Clinical Centre, University of Szeged, Szeged, Hungary; [2]Department of Neurology, Faculty of Medicine, Szent-Gyorgyi Albert Health Centre, University of Szeged, Szeged, Hungary; [3]Faculty of Medicine, Institute of Behavioural Medicine, Szent-Gyorgyi Albert Health Centre, University of Szeged, Szeged, Hungary.

Introduction
Clinical studies revealed an increased incidence of migraine attacks in conditions with falling levels of plasma oestrogen in the perimenstrual phase of the menstrual cycle and during the hormone-free interval in women taking combined oral contraceptives.
Objective
The purpose of the study was to assess the connection between menstrual cycle, bleeding patterns of women with migraine and the clinical characteristics of the migraine attacks.
Methods
The questionnaire-based survey ($n=186$) was undertaken in the South-Eastern Hungary with the collaboration of the Department of Neurology and the Department of Obstetrics and Gynaecology. We invited all women with M0 and MA in the Outpatient Headache Unit of the Department of Neurology, Szeged, Hungary to participate in the questionnaire-based study. We collected a data in two time periods: between 2006–2009 and 2013–2014. We collected the answers via three ways: personal face-to-face interviews, online and postal way. The main outcome measures were to describe the menstrual pattern of women with migraine, the relationships between menstrual cycle and clinical characteristics of the migraine attacks.
Results
Our study group consisted of 108 (52%) women with M0 and 78 (48%) women with MA. The average age of the patients at the diagnosis of migraine was 18.79 ± 6.97 years. The Pearson's correlation test revealed a relationship between duration of menstrual cycle and the intensity of headache pain ($P=0.012$). However, there was no significant relation between the intensity of headache pain and other study parameters (e.g. duration of use of COC, length of bleeding, menstrual cramps, amount of bleeding, and BMI).
Conclusions
According to our best knowledge this is the first study in Hungary to describe contraceptive habits of migraineurs and the connection between the duration of menstrual cycle and intensity of the migraine head pain.

DOI: 10.1530/endoabs.37.EP136

EP137

Constitutive and inducible regulation of PEPCK isoform genes in human cells

Venu Seenappa[1], Manjunath B Joshi[1], Bidyadhar Das[2] & Satyamoorthy Kappaettu[1]
[1]School of Life Sciences, Manipal, Udupi, Karnataka, India; [2]Northeast Hill University, Shillong, Meghalaya, India.

Introduction
Phosphoenolpyruvate carboxykinase (PEPCK) is the key rate determining enzymes of gluconeogenesis pathway. PEPCK exists in cytosolic (PEPCK-C) and mitochondrial (PEPCK-M) isoforms. PEPCK isoforms maintain glucose/lipid homeostasis and is being explored as a therapeutic target for treating metabolic diseases. We tested the influence of a naturally occurring compound Genistein (a soy derived isoflavone) to constitutively regulate PEPCK isoforms to address its potential use as a therapeutic molecule.
Methods
HepG2 and fibroblasts were tested for the effects of genistein by western blot; RNA stability was examined by RT-PCR using actinomycin treated cells; transcriptional regulation was performed by reporter assays and CpG DNA methylation was analysed by bisulfite sequencing.
Results
Expression and activity of PEPCK isoforms in fibroblasts was lower than in HepG2 hepatoma cells. In HepG2 cells, genistein induced degradation of PEPCK-C transcript and proteins but increased PEPCK-M expression. In fibroblasts, genistein increased PEPCK-C expression through promoter demethylation but PEPCK-M was unaffected. Reporter gene and RT-PCR assays suggested genistein mediated RNA degradation of PEPCK-C in HepG2 cells is due to the existence of AU-rich elements (AREs) in 3′-UTR of the gene.
Conclusion
We show an evidence for the regulation of PEPCK-C gene by promoter DNA methylation in human fibroblasts, which might be responsible for maintaining baseline PEPCK activity in non-gluconeogenic tissues. We show selective effect of soy isoflavone genistein on PEPCK isoform genes in hepatic and extra hepatic cell types by increasing the expression of PEPCK-M as a compensatory mechanism and there by maintaining glucose homeostasis in cells as a pro-survival effect.
Disclosure
Department of Biotechnology, Government of India.
DOI: 10.1530/endoabs.37.EP137

EP138

Study on the correlation between serum androgens and sexual function in post-menopausal women

Soheila Nazarpour[1], Masome Simbar[1], Fahimeh Ramezani Tehrani[2], Maryam Tohidi[3] & Hamid Alavi Majd[4]
[1]Midwifery and Reproductive Health Department, Faculty of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences and Health Services, Tehran, Iran; [2]Research Institute for Endocrine Sciences, Reproductive Endocrinology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [3]Research Institute for Endocrine Sciences, Prevention of Metabolic Disorders Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [4]Biostatistics Department, Faculty of Paramedicine, Shahid Beheshti University of Medical Sciences and Health Services, Tehran, Iran.

Introduction
Sexual dysfunction could be under the influence of menopause and the changes it causes in hormone levels. The purpose of this study is to examine the correlation between serum levels of androgens and sexual function in post-menopausal women.
Methods
This is a community-based, descriptive-analytical study involving 405 post-menopausal women, aged 40–65 years, who had reached menopause up to 3 years prior to the study. A multi-stage, randomized sampling was conducted in the cities of Chalous and Nowshahr. The data was collected using the female sexual function index (FSFI) questionnaire, a researcher-made questionnaire, and blood sampling to study the serum levels of androgens (testosterone and DHEAS), sex hormone-binding globulin (SHBG), and oestradiol in the laboratory. The acquired data was analysed statistically using SPSS.
Results
61% of the subjects were suffering from female sexual dysfunction (FSD). Total testosterone levels had a negative correlation with scores in the domain of desire ($r=-0.108$, $P=0.029$), DHEAS levels were positively correlated with scores in the domain of pain ($r=0.113$, $P=0.022$), and the free estradiol index (FEI) was positively correlated with scores in the domain of pain ($r=0.115$, $P=0.020$). Satisfaction with marital relationship had a significant positive correlation with total testosterone levels ($r=0.131$, $P=0.008$) and the free androgen index (FAI) ($r=0.100$, $P=0.044$). In examining the correlation between FSFI scores and hormone levels, multiple regression analysis showed that serum levels of total testosterone and free androgen index were predicting factors in, respectively, the domain of lubrication ($P=0.042$) and satisfaction ($P=0.021$).
Conclusion
Androgenic hormones can affect certain aspects of sexual function in post-menopausal women. This subject area, however, requires further investigation.

DOI: 10.1530/endoabs.37.EP138

EP139

Increased circulating urocortin-3 levels is associated with polycystic ovary syndrome

Muzaffer Temur[1], Özgür Yilmaz[1], Saliha Aksun[2], Pelin Özün Özbay[3], Mehmet Calan[4], Tuncay Küme[5], Murat Karakulak[6] & Hüseyin Anil Korkmaz[7]
[1]Department of Obstetrics and Gynecology, Manisa Merkezefendi State Hospital, Manisa, Turkey; [2]Department of Medical Biochemistry, Izmir Katipcelebi University Medical School, Izmir, Turkey; [3]Department of Obstetrics and Gynecology, Aydin Obstetrics and Pediatrics Hospital, Aydin, Turkey; [4]Department of Endocrinology, Izmir Bozyaka Education and Research Hospital, Izmir, Turkey; [5]Department of Medical Biochemistry, Dokuz Eylul University Medical School, Izmir, Turkey; [6]Department of Obstetrics and Gynecology, Silivri State Hospital, Istanbul, Turkey; [7]Division of Pediatric Endocrinology, Dr Behçet Uz Children Research and Training Hospital, Izmir, Turkey.

Purpose
This study aims to compare serum urocortin-3 levels in women with PCOS and healthy women, and establish what role urocortin-3 levels play in PCOS.
Methods
Fifty-two patients with PCOS and 55 healthy women were included in the study, matched for age and BMI. Fasting blood glucose (FBG), insulin, hs-CRP, urocortin-3, and free testosterone levels of the all participants were measured. HOMA-IR was used to calculate the insulin resistance.
Results
Circulating urocortin-3 levels were significantly increased in women with PCOS than in control subjects (54.49 ± 5.77 pmol/l vs 51.28 ± 5.86 pmol/l, $P=0.005$). Urocortin-3 levels positively correlated with hs-CRP in PCOS group ($r=0.391$, $P=0.004$). There was no any correlation between urocortin-3 and other parameters. Multivariable binary logistic regression analysis showed that elevated urocortin-3 levels were associated with PCOS. Receiver operating characteristic curve analysis showed that urocortin-3 levels were useful as a diagnostic marker for PCOS. The optimal cut-off value of urocortin-3 for detecting PCOS was ≥ 51.46 pmol/l, at which the sensitivity was 75% and specificity was 68%.
Conclusions
Circulating concentration of urocortin-3 are significantly increased in women with PCOS. Furthermore, increased urocortin-3 levels were associated with PCOS after adjustment for potential confounders. This link in between urocortin-3 and PCOS may be due to an underlying chronic inflammation in subjects with PCOS.

DOI: 10.1530/endoabs.37.EP139

EP140

Implication of non polar phytocomponents of aloe vera gel in management of polycystic ovarian syndrome

Laxmipriya Nampoothiri, Radha Maharjan & Arpi Dey
M S University of Baroda, Vadodara, India.

Background
Aloe vera gel has been proven to have hypoglycaemic, hypolipidemic, and steroid enzyme regulating properties. These are of clinical significance in reproductive pathology namely polycystic ovary syndrome (PCOS). Preliminary, '*in-vitro*' studies suggested that non-polar component is responsible for the steroid enzyme modulating effect. This study investigates the role of non polar phytocomponent's of aloe vera gel, which could be responsible in management of this pathology.
Aim
The aim of this study was to evaluate the effects of non-polar phyto-components on the PCOS pathology using rodent model.
Design and methods
Rodent model was developed using letrozole (0.5 g/kg body weight daily orally for 21 days) and validated for PCOS pathology. Later, the non-polar component, extracted using petroleum ether (containing phytosterols validated by HPTLC) was administered to PCOS rats daily ($\sim$25 μg/kg body weight) for 2 months, with respective controls (Aloe and vehicle). After the course of treatment, ovarian expression profile (mRNA and protein) of major steroidogenic genes namely StAR, 3 beta-hydroxysteroid dehydrogenase (3β-HSD), aromatase, LHR, and FSH-R were monitored in addition to biochemical parameters. Parallely, phytochemical elucidation of non-polar fraction was evaluated.
Results
Expression of StAR, 3β-HSD, and LHR was found to be decreased ($P<0.01$), both at transcript as well as protein level in non-polar fraction treated PCOS group as compared with untreated PCOS control while other genes studied did not show any significant change. Phytochemically, aloe vera non-polar fraction exhibited the presence of β-sitosterol in major quantity, along with minor amounts of stigmasterol, lupeol, and its derivatives.
Conclusion
Non-polar fraction of aloe vera gel has a potential to manage PCOS phenotype, by modifying steroidogenic targets. This study may serve as platform for designing drugs by exploring these novel targets.
Disclosure
This work was supported partly by University Grants commision, India (F.no: 41-1276/2012(SR) and by Department of Science and Technology (SB/SO/HS-190/2013).

DOI: 10.1530/endoabs.37.EP140

EP141

Abstract withdrawn.

DOI: 10.1530/endoabs.37.EP141

EP142

Is idiopathic hirsutism associated with an increase in metabolic disturbances?

Samira Behboudi-Gandevani[1], Fahimeh Ramezani Tehrani[1], Masoomeh Simbar[3] & Fereidoon Azizi[2]
[1]Research Institute for Endocrine Sciences, Reproductive Endocrinology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [2]Endocrine Research Center, Shaheed Beheshti University of Medical Sciences, Tehran, Iran; [3]Department of Reproductive Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Introduction
Idiopathic hirsutism (IH) is one of the most frequent complaints affecting 13% of reproductive aged women. The relationship between IH and metabolic abnormalities are not fully understood. The aim of this study was to evaluate the relationship between IH and metabolic abnormalities.
Methods
A total number of 100 idiopathic hirsute women (range 15–45 years) recruitment from a population based cohort study of Tehran Lipid and Glucose Study. Control age-matched women were selected from the same population. Biochemical characteristics of the participants including waist and hip circumferences and ratio, blood pressure, glucose, androgens and lipid profiles, and insulin resistance by HOMA-IR were compared. Differences between the two groups in univariate analysis were detected by independent Student's *t*-test for continuous variables with normal distribution or by the Mann–Whitney *U* test for those without normal distribution. Analysis of covariance (ANCOVA) was used for comparison of groups with adjustment for the BMI.
Results
The IH subjects had higher BMI and waist to hip circumferences ratio compared with healthy controls, 25.4 (3.2) and 0.83 (0.04) in IH vs 23.9 (4.2) and 0.81 (0.05) in controls ($P=0.02$ and $P=0.04$) respectively. The mean fasting insulin, HOMA-IR, and TG in IH women were statistically higher than in controls but there were not any statistical differences between them and other biochemical, anthropometric, lipid, and blood pressure profiles after adjustment for age and BMI.
Conclusions
Our data suggest that IH did not associate with metabolic disturbances. It seems that no more additional intervention and evaluation are needed in IH subject later in life.

DOI: 10.1530/endoabs.37.EP142

EP143

Prevalence and pattern of menstrual disorders and related factors among Iranian women in reproductive ages: a population based study

Marzieh Rostami Dovom[1], Fahimeh Ramezani Tehrani[1], Maryam Farahmand[1], Somayeh Hashemi[1] & Freydoun Azizi[2]
[1]Research Institute for Endocrine Sciences, Reproductive Endocrinology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [2]Research Institute for Endocrine Sciences, Endocrine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Introduction
Menstrual disturbances can be considered as a sign of reproductive system disorders in women in reproductive ages. These disturbances can be indicators of serious underlying problems. The aim of this study was to determine the prevalence and pattern of menstrual related manifestation among Iranian women.
Methods
This was a population-based study conducted among women ($n=941$) aged 18–45 years. The participants who met the eligibility criteria were selected from four provinces using quota stratified cluster sampling, and invited for further comprehensive interview.
Results
The most common menstrual disorders in Iranian women were dysmenorrhea (67/5%) and premenstrual syndrome (54/9%) respectively. Prevalence of other non-anatomical abnormal uterine bleeding was 19.9%. Some demographic factors such as younger age, married at older ages, as well as celibacy was correlated with the incidence of dysmenorrheal ($P<0.5$). The results have shown that more than 83% of women younger than 25 years old suffer from dysmenorrheal. Younger women (<25 years) are 2.3 times as likely to have dysmenorrheal than women 25 years and older (OR=2.3, 95% CI: 1.5–3.7, $P<0.0001$). Also, never married women are 2.1 times as likely to have dysmenorrhea than married women (OR=2.1, 95% CI: 1.2–3.6, $P<0.0001$). Higher BMI and higher levels of education had a significant relationship with oligomenorrhea and premenstrual syndrome respectively ($P<0.5$). The result of this study has shown that younger menarche age was significantly associated with the occurrence of menorrhagia.
Conclusion
Almost one out of every four Iranian women in reproductive age suffers from at least one menstrual disorder. Encouraging women to change lifestyles in reproductive ages, counselling and giving adequate information on menstrual disorders can play a main role in reducing the adverse effects of these disorders.

DOI: 10.1530/endoabs.37.EP143

EP144

Testosterone level in men correlates with BMI and cardiorespiratory fitness but is not related to age

Laura DeFina[2], Nina Radford[3], David Leonard[2], Erica Howard[2], Rick Wilson[3], Tyler Cooper[2], Michael Clark[3] & Ugis Gruntmanis[1]
[1]University of Texas Southwestern, Dallas, Texas, USA; [2]The Cooper Institute, Dallas, Texas, USA; [3]Cooper Clinic, Dallas, Texas, USA.

Background
Presently it is unknown how much of testosterone decline associated with aging is actually due to ageing *per se*, and how much is related to weight gain, decreased activity, and other age-related factors. Understanding the modifiable factors associated with low testosterone, such as obesity or cardiorespiratory fitness (fitness) is critical.
Methods
The observational, cross-sectional study included 1653 men, ≥50 and <80 years of age, seen between January 2012 and December 2012 for a preventive medical examination and underwent BMI, total testosterone, and objective fitness measurements as defined by the total duration of time on a maximum Balke treadmill test. Treadmill time was then used to estimate metabolic equivalents (METs). All participants underwent morning (0700–0900 h) total testosterone measurement using the standard chemiluminescence method. Testosterone thresholds were categorized into low (<250 ng/dl), low normal (250–<400 ng/dl), and normal (≥400 ng/dl). We used traditional sample statistics to summarise characteristics of the sample within decades of age and ordered categories of BMI.
Results
While levels of mean testosterone levels in all age groups were in the normal range were statistically different between groups, (50–59 years, testosterone mean=479.0 ng/dl (S.D.=175.4); 60–69 years, testosterone mean=457.2 ng/dl (S.D.=204.1); and 70–79 years, testosterone mean=464.6 ng/dl (S.D.=176.7); trend P value=0.05), although, the trend was statistically different, mean testosterone levels in all groups were in the normal range. The prevalence of low testosterone did not significantly differ between 50–59, 60–69, and 70–79 age groups (<250 ng/dl=7.6–9.3% to 8.7%; trend test $P=0.17$) but did change with increasing BMI, (<250 ng/dl=3.4–6.8% to 17.8%; trend test $P<0.001$). Finally, fitness was positively correlated with total testosterone levels ($P<0.001$) and this correlation persisted after adjustment for age and BMI.
Conclusion
In this group of generally healthy men, there was no decrease in the mean total testosterone level with increasing age, yet we found statistically and clinically negative correlation between testosterone and BMI and positive correlation between testosterone and fitness.

DOI: 10.1530/endoabs.37.EP144

EP145

Analysing by decade, testosterone undecanoate depot injectable does not increase prostate volume: study during up to 7 years on hypogonadic patients

Matei Pisoschi[1], Mara Carsote[2], Catalina Poiana[2], Dana Cristina Staicu[3] & Dan Peretianu[3]
[1]Hospital 'Th. Burghele', Bucharest, Romania; [2]Institute of Endocrinology, Bucharest, Romania; [3]Societatea Civila Medicala 'Povernei', Bucharest, Romania.

Aim
Re-analysing the effect of injectable testosterone undecanoate depot (TUD) in hypogonadic patients.
Materials and method
(A) Patients: at onset 210 men with hypogonadism (median age: 61.5 years). (B) Distribution: by decade; $n=4$, 12, 21, 54, 59, 43, 16, and 1. (C) TUD (NebidoR-Bayer-Schering) 1000 mg was injected one per 3 months i.m. (D) Prostate volume (PV) appreciated by per-abdominal ultrasound: 3.5 MHz probe, elliptical volume (cm^3), Aloka 550. (E) Time of analysis: before starting testosterone (T0), after ½ month (T1), 3 months (T2), 6 months (T3), 1 year (T4), 2 years (T5), 3 years (T6), 4 years (T7), 5 years (T8, $n=28$), 6 years (T9, $n=12$), and 7 years (T10, $n=6$). (F) Maximum increment from T0 was noted Δ M %. Average increment was noted A %. (G) Statistical analysis: Student' t-test.
Results
i) All average prostatic volume for decade in figure. Maximum increment (Δ M %) per decade (45.95; 20; 40.35; 42.5; 45.45; 64.41; and 39.56), including the moment (Δ M % at) and average increment (Δ A %) (Table). (II) PV at T0 increases with age, from minimum 15.38 (19–29 years) to maximum 47.41 (80–89 years), $P=0.0007$. (III) Considering all observations (some at 5/6/7 years), TUD did not increase PV significantly (in fact the average of increment in all patients was negative=−12.54%). Δ M % per decade: 20. (IV) Inside a specific decade no significant increase in PV was registered: all $P>0.05$; exception: 80–89 decade, $P=0.002$, at 3–5 years. (V) In some patients, especially from 50 to 79 years, TUD could decrease slightly prostatic volume.
Conclusions
Considering the risk for prostate (in elderly), testosterone undecanoate 1000 mg depot injectable is a safe treatment, even after 3–7 years of administration. Precautions should be accorded to men over 80 years old, after the 3rd year administration.

DOI: 10.1530/endoabs.37.EP145

EP146

Testosterone undecanoate 1000 mg at 3 months did not increased prostatic specific antigen level: January 2015

Matei Pisoschi[1], Mara Carsote[2], Catalina Poiana[2], Dana Cristina Staicu[3] & Dan Peretianu[3]
[1]Hospital 'Th Burghele', Bucharest, Romania; [2]Institute of Endocrinology, Bucharest, Romania; [3]Societatea Civila Medicala 'Povernei', Bucharest, Romania.

Aim
To find if testosterone undecanoate (TUD) 1000 mg injection (NebidoR; Bayer-Schering) at 3 months has a negative effect on prostate.
Materials and method
i) PSA (ng/ml) registred before (T0) and after TUD at T1 (2 weeks) to T10 (7 years) (see Pisoschi, this Congress); ii) statistical analysis: *t*-test, simple correlation, and multiple regression.
Results
(A) Patients at onset: 143 men, 18–96 years, average: 60.38; median: 60. (B) Prostatic volume before TUD (cmc): average: 34.81; in evolution (see Pisoschi, this Congress). (C) Average PSA (no patients): before TUD = 1.59 (143); at 1 year = 1.69 (99); 2 years = 1.4 (73); 3 years = 1.85 (48); 4 years = 2 (38); 5 years = 1.86 (26); 6 years = 1.51 (10); and 7 years = 2.86 (6). (D) Statistical difference of average: nonsignificant for all the times from 2 weeks to 7 years. (E) Correlation between age and PSA was: i) significant before and after treatment till 2 years but nonsignificant for 3–7 years (PSA did not change as age after treatment). (F) Correlation between PSA and prostatic volume was significant, both before and after treatment (depending on group size); r before TUD = 0.56, at 1 year = 0.51, 2 years = 0.55, 3 years = 0.42, 4 years = 0.11, 5 years = 0.57, 6 years = −0.06, and 7 years = 0.52. (G) Multiple regression test ($r^2 = 0.53$–0.99, $F = 36.36$–4906) shows that PSA level post testosterone does not depend on testosterone but on age, prostatic volume (before and after treatment), and PSA initial level (before testosterone administration); $p \ll 0.001$.
Conclusions
i) Testosterone undecanoate 1000 mg injectable i.m. at 3 months did not increase PSA level after 7 years administrations. ii) PSA level post testosterone was in fact dependent only on age, prostatic volume before treatment and PSA level before treatment.

DOI: 10.1530/endoabs.37.EP146

EP147

Role of elevated serum adiponectin in delayed puberty of thalassemic patients

Mohamed Mekawy, Merhan Nasr, Soha Youssef, Mahira Almogy & Nevine Gamal
Ain Shams University, Cairo, Egypt.

Background
Adipose tissue dysfunction can play a role in the neuroendocrine and haematopoietic dysfunctions affecting thalassaemic patients.
Aim of the work
In this work, we aimed to study the serum levels of adiponectin, an adipocytokine, in Egyptian β-thalassemia patients in relation to their endocrinal complications.
Subjects and methods
The study included 60β-thalassaemia patients; (major, intermedia, and minor) and 30 healthy age- and sex-matched controls. The diagnosis of thalassemia was based on clinical, haematological, and genetic studies. Anthropometric measurements, clinical neuroendocrinal assessment, iron profile (serum ferritin, serum iron, and total iron binding capacity) and measurment of serum levels of adiponectin using ELISA were performed for all subjects. Our β-thalassemia major and intermedia patients had significantly lower BMI, shorter height, lower weight, delayed growth and puberty while thalassemia minor patients showed no significant delay in puberty compared with healthy controls.
Results
A significantly higher level of adiponectin was found in thalassemic patients (median = 3.5 ng/ml) compared to controls (median = 0.4 ng/ml) with the level becoming progressively higher with degree of clinical severity (median = 0.6 ng/ml in minor, 2.5 ng/ml in intermedia, and 4.3 ng/ml in major). The level of adiponectin was negatively correlated to height, weight, and BMI in both thalassemia intermedia and major while it was negatively correlated to puberty only in thalassemia major patients. A clinically significant level of adiponectin was obtained at >0.8 ng/ml for delayed puberty and iron overload (high serum iron and serum ferritin).
Conclusion
We found that high adiponectin levels correlated to iron overload and delayed growth in both β-thalassemia major and intermedia patients as well as to delayed puberty in thalassemia major.

DOI: 10.1530/endoabs.37.EP147

EP148

Prevalence of autoimmune thyroid markers in euthyroid women with polycystic ovary syndrome

Ahmed Bahaa El-Din, Alyaa El-Sherbeny & Emad Abd El-Hadi
Ain Shams University Hospital, Cairo, Egypt.

Introduction
Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women in reproductive age. A condition that causes irregular menstrual periods because monthly ovulation is interrupted and levels of androgens are elevated. It occurs in about 5–10% of women and is considered to be the most common cause of anovulatory infertility in reproductive age.
Objectives
To compare the prevalence, levels of thyroid auto-antibodies in a group of Egyptian women with PCOS and a control group in reproductive age to determine whether women with PCOS have a greater risk of thyroid autoimmune diseases, thyroid dysfunction or not.
Patients and methods
This study was conducted on 45 euthyroid women with PCOS and 18 healthy women as a control in the Outpatient Clinics of Endocrinology, Ain Shams University Hospital. PCOS was defined by the revised 2003 Rotterdam criteria. Thyroid function was evaluated by measurement of TSH and FT_4 levels, anti-thyroid peroxidase, and anti-thyroglobulin antibodies (anti-TPO and anti-TG respectively) as markers for thyroid autoimmunity. All parameters were measured using electrochemiluminescence immunoassay.
Results
Women with PCOS had a significantly higher levels of anti-TPO in comparison to controls (27 ± 10 and 21 ± 10 IU/ml, respectively; $P < 0.05$) with no significant difference in anti-TG, TSH, or FT_4 between the two groups. Patients with PCOS had a non-significant higher prevalence of positive anti-TG and/or anti-TPO in comparison to controls (40 and 22.2%, respectively; $P > 0.05$), anti-TPO alone (28.9 and 16.7, respectively; $P > 0.05$), and anti-TG alone (22.2 and 11.1%, respectively; $P > 0.05$).
Conclusions
Women with PCOS had a significantly higher levels of anti-TPO than controls that may put them at a higher risk for thyroid autoimmune disease.

DOI: 10.1530/endoabs.37.EP148

EP149

Stereoselective effects of statins on xenobiotic-metabolising pathways

Martina Korhonova & Zdenek Dvorak
Department of Cell Biology and Genetics, Faculty of Science, Palacky University, Slechtitelu 11, 783 71 Olomouc, Czech Republic.

Several of currently used drugs are chiral compounds. Majority of them are clinically administered as a racemic (equimolar) mixture of enantiomers. Individual enantiomers of one drug can qualitatively and quantitatively differ in their biological activities (pharmacology, toxicology, pharmacokinetics, etc.). Therefore, enantiopure drugs have been developed and introduced to the therapy. Statins are drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase. Atorvastatin, rosuvastatin, and fluvastatin are the most often prescribed statins. They have two chiral centres, thus they form four enantiomers (3R5R, 3R5S, 3S5R, and 3S5S). They are marketed as a racemic mixture of these enantiomers; however their enantiopure forms have been introduced to clinic recently (3R5R-atorvastatin, 3R5S-rosuvastatin, and 3R5S-fluvastatin). In this study, we investigated enantiospecific interactions of all four enantiopure forms of atorvastin, rosuvastatin, and fluvastatin with main transcriptional regulators of drug-metabolizing enzymes – aryl hydrocarbon receptor (AhR), glucocorticoid

receptor (GR), and pregnane X receptor (PXR). Agonist and antagonist activities of tested compounds towards AhR, PXR, and GR were determined using human reporter cell lines. Moreover, we have tested enantiospecific effects of statins on the expression of drug-metabolising enzymes CYPs on mRNA and protein level in primary human hepatocytes.

Disclosure

Financial support from Czech Scientific agency 13-01809S and Students project of Palacky University Olomouc PrF-2015-003 is greatly acknowledged.

DOI: 10.1530/endoabs.37.EP149

EP150

Serum N-terminal pro-B-type brain natriuretic peptide levels detection and cardiac interventricular septum tissue Doppler echocardiographic evaluation of women with polycystic ovary syndrome

Mehmet Emin Ayhan[1], Senay Arikan Durmaz[2], Ayse Carlioglu[2] & Selami Demirelli[2]

[1]Erzurum Regional Training and Research Hospital, Erzurum, Turkey; [2]Dörtyol Government Hospital, Hatay, Turkey.

Introduction

The aim of this study, left ventricular systolic and diastolic function by echocardiography and tissue Doppler echocardiographic evaluation and relationship serum N-terminal pro-B-type brain natriuretic peptide (NT-proBNP) levels of women with polycystic ovary syndrome (PCOS).

Materials and method

Thirty-two women with PCOS (age: 23.4–4.6 years; BMI: 23.8–4.8 kg/m^2), similar age and BMI have features 30 healthy womens controls involved in the study. Anthropometric features, NT-proBNP levels, HOMA-IR index, renal and hepatic function parameters, serum lipid and cholesterol levels, hormonal tests were measured. Interventricular septum was evaluated by tissue Doppler echocardiography. Statistical Package for the Social Sciences (SPSS) 17 programme was used in the statistical analysis of data. Student's *t*-test, Pearson's correlation test, and multiple regression analyse test results of all the parameters stuided in the PCOS and control group. İmportance level of values whose P value <0.05 is taken as statiscally significantly.

Results

PCOS group had NT-proBNP ($P=0.04$), total testosterone ($P=0.005$), cholesterol ($P=0.02$), and triglycerides ($P=0.006$) levels higher than control group. Echocardiographic assessment of the interventricular septum thicknes and width of the aortic root measurements levels in the PCOS group higher than the control group. Also, left ventricular mitral valve E-wave velocity ($P=0.039$) in the PCOS group were significantly less than the control group and left ventricular deseleration time ($P=0.035$) longer than control group. PCOS group with multiple regression analysis when the high NT-proBNP levels was positively correlated with age ($r=0.364$, $P=0.002$), interventricular septum thicknes (İVST) ($r=0.299$, $P=0.02$), and width of aortic root ($r=0.272$, $P=0.025$).

Conclusions

Our study results have shown that, NT-proBNP levels have able to a biochemical cardiac early marker of diagnosis subclinical diastolic dysfunction in younger women with PCOS. Early time examined by conventional echocardiography and tissue Doppler echocardiography possibly to helpful determinate early diastolic dysfunction of women with PCOS.

DOI: 10.1530/endoabs.37.EP150

EP151

The effects of endocrine disruptors on the *in vitro* hormone regulation of rat pituitary

Zsuzsanna Valkusz[1], Marianna Radács[2], Regina Pálföldi[2], Zoltan Molnar[2], Krisztián Sepp[1], Anna László[2], Tamás Alapi[3] & Marta Galfi[2]

[1]First Department of Medicine, Szeged, Hungary; [2]Department of Environmental Biology and Education of Gyula Juhasz, Faculty of Education, Szeged, Hungary; [3]Department of Inorganic and Analytical Chemistry, Faculty of Science and Informatics, Szeged, Hungary.

Endocrine disruptor compounds (EDCs) may cause disorders and alter the normal hormone synthesis and/or release.

Aim was to investigate the effects of EDCs on normal hypophysis regulation; particularly the arginine–vasopressine (AVP) activated ACTH release from adenohypophysis cells and the monoamine activated AVP release from neurohypophysis cells.

Primary monolayer cell cultures prepared from Wistar rat hypophyses. Separated adenohypophysis (AdH) and neurohypophysis (NH) tissues were dissociated by enzymatic and mechanic methods. The 14-day-old cultures were standardized for ACTH in AdH for AVP in NH cultures and for cell-viability. ACTH and AVP contents of the endocrine cells were checked and the hormone release function was challenged with an aspecific osmotic stimulus (30 mM K^+). Untreated cultures used as control. Cultures treated – (I) 1 h 0.1 μg/ml EDCs (ClB, MU, DU, and PU)/$n=8$; (II) 10^{-6} M monoamines (epinephrine: A; serotonine: 5HT) alone/$n=8$; and (III) the stimulant agents (AVP, monoamines) in combinations with EDCs/$n=8$. ACTH and AVP and protein content was measured from supernatant media.

Results

Basal ACTH (1470 pg ACTH/mg protein) and AVP (47.25 pg AVP/mg protein) from AdH and NH respectively did not change significantly after the EDCs (I) treatment. The AVP induced ACTH release (11 750 pg ACTH/mg protein) and the monoamines induced AVP (5HT: 194.18 pg AVP/mg protein and A: 199.26 pg AVP/mg protein) (II) became strongly increased.

In the (III) experimental protocols, combined treatments where were used (AdH/ACTH: AVP+ClB: 14 620 pg ACTH/mg protein; AVP+PU: 13 114 pg ACTH/mg protein; AVP+MU: 14 997 pg ACTH/mg protein; AVP+DU: 15 174 pg ACTH/mg protein; NH/AVP: A+CLB: 216.16 ng AVP/mg protein; 5HT+CLB: 203.28 pg AVP/mg protein; A+PU: 173.29 pg AVP/mg protein; 5HT+PU: 163.42 pg AVP/mg protein; A+MU: 184.66 pg AVP/mg protein; 5HT+MU: 181.39 pg AVP/mg protein; A+DU: 211.28 pg AVP/mg protein; and 5HT+DU: 216.88 pg AVP/mg protein).

Data demonstrate that EDCs can moderate pituitary cell regulation *in vitro*. AVP and monoamine regulated hormone release from hypophyseal cells was influenced variably depending from the EDCs applied.

Disclosure

Supported by TÁMOP 4.1.1.C-12/1/KONV; TÁMOP-4.2.2.A-11/1/KONV-2012-0035.

DOI: 10.1530/endoabs.37.EP151

EP152

Endocrine disruptive effect of plastic byproduct bisphenol A on GH activity

Fahad Zadjali, Mohammed Al Masroori & Mohammed Habais

Sultan Qaboos University, Muscat, Oman.

Bisphenol A (BPA) is a byproduct of polycarbonate plastic widely present in food containers. BPA is historically a known endocrine disruptor and due to its oestrogen agonist activity, BPA consumption is associated with hypothyroidism and reproductive disorder. Recent studies have shown that oestrogen antagonised GH actions. Since BPA has oestrogen agonist activity, the effect of BPA exposure on GH activity has not yet been investigated.

Aim

To study the *in vivo* effect of acute/chronic consumption of BPA on long body growth and *in vitro* effect of BPA on cellular GH signalling.

Method

CD-1 mice treated with BPA (1.75 mM orally) for 3 months starting from weaning (day 20). Body weight, tail length, and tibia length were monitored weekly. Liver tissue were collected 15 min after injection of GH or PBS.

Results

Mice given BPA in drinking water showed significant reduction in body weight from days 30 to 60 compared to control littermate. However, as result of catch-up growth, the BPA-treated mice weight became similar to control after day 60. Similar changes were observed in tibia length in which mice treated with BPA had significantly shorter tibia on days 30–50 and started to rise. Chronic treatment of BPA increased expression of SOCS2, which is a known cellular inhibitor of GH signalling.

Conclusion

In humans, there is a dramatic decrease in longitudinal bone growth, which begins during intrauterine life and is interrupted briefly at puberty. Here we found for first time that exposure to BPA, a plastic byproduct, interrupt linear growth with downregulation of GH signalling and mice exposed to BPA exhibit supranormal linear growth phenomenon known as catch-up growth. Further investigation is need to study the effect of BPA on the metabolic action of GH specially those related to body fat content and impact on increasing world epidemic of obesity.

DOI: 10.1530/endoabs.37.EP152

EP153

A possible link between LH and macrophage migration inhibitory factor levels in polycystic ovary syndrome

Mehmet Calan[1], Tuncay Kume[2], OzgUr Yilmaz[3], Tugba Arkan[1], Gokcen Unal Kocabas[4], Ozge Dokuzlar[5], Kemal Aygun[5], Mehmet Asi Oktan[5], Nilay Danıs[5] & Muzaffer Temur[3]
[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Dokuz Eylul University Medical School, Izmir, Turkey; [2]Department of Medical Biochemistry, Dokuz Eylul University Medical School, Izmir, Turkey; [3]Department of Obstetrics and Gynecology, Manisa Merkezefendi Hospital, Manisa, Turkey; [4]Division of Endocrinology and Metabolism, Department of Internal Medicine, Izmir Bozyaka Training and Research Hospital, Izmir, Turkey; [5]Department of Internal Medicine, Dokuz Eylul University Medical School, Izmir, Turkey.

Purpose
Macrophage migration inhibitory factor (MIF) is a multi-functional cytokine which plays a role in metabolic and inflammatory processes. Increasing evidence suggests that there is a link between MIF and ovulation. We aimed to evaluate plasma MIF levels in women with polycystic ovary syndrome (PCOS) and to determine whether MIF levels differ between the follicular phase and mid-cycle of the menstrual cycle in eumenorrheic women.
Methods
Ninety women with PCOS and 80 age- and BMI-matched healthy eumenorrheic women were consecutively recruited into this prospective observational study. For all subjects, plasma MIF levels in early follicular phase were measured by ELISA; for the 40 healthy controls, MIF levels were also measured during mid-cycle of the same menstrual cycle.
Results
Plasma MIF levels were significantly higher in women with PCOS than in eumenorrheic women (14.16 ± 1.59 ng/ml vs 10.39 ± 0.70 ng/ml; $P<0.001$). MIF levels were significantly higher at mid-cycle than in the follicular phase in eumenorrheic women (11.15 ± 0.61 ng/ml vs 10.56 ± 0.82 ng/ml; $P<0.001$). MIF was positively correlated with BMI, hs-CRP, and HOMA-IR in both groups. MIF was positively correlated with LH and free-testosterone only in the PCOS group. Binary logistic regression analyses revealed that the odds ratio (OR) for PCOS independently increases linearly with elevated MIF (OR = 1.385, 95% CI = 1.087–1.764, $P=0.017$).
Conclusion
MIF may play a crucial role in the reproductive system in women, including the development of PCOS and normal ovulation.

DOI: 10.1530/endoabs.37.EP153

EP154

Analysis of gonadal steroid secretion in the serum of women during ovarian stimulation

Marie Claude Menet[1,2], Guillaume Damiens[1], Erwan Méténier[1], Nacéra Sraouia[1], Marie Clémence Leguy[1], Vanessa Gayet[1] & Jean Guibourdenche[1,2]
[1]AH-HP, Paris, France; [2]Université Paris Descartes, Paris, France.

Introduction
Biochemical follow up of the ovarian function after ovarian stimulation is restricted to the measurement of serum oestradiol and progesterone. We aim to investigate the entire ovarian steroidognesis after ovarian stimulation.
Materials and methods
50 women (26 IVF and 24 ICSI) who underwent AMP induction (based on rFSH stimulation after GnRH agonist or antagonist) for the same cause of infertility were retrospectively involved and compared to 11 IUI (control). Oestrogens (oestrone, oestradiol, and oestriol), androgens (Δ4-androstenedione and testosterone), and progestatives (progesterone and 17 hydroxyprogesterone) were measured using immunoassay (RIA and CobasR Roche) each 48 h (days 5–13 in AMP and days 8–14 in control). Steroid profiles were characterized using mass spectrometry. Results are expressed as median values and a $P<0.05$ was considered significant.
Results
Steroids basal secretion was within the normal range (IVF, ICSI, and IUI respectively): oestradiol (223, 317.5, and 314 pmol/l), testosterone (1124.5, 903.5, and 1606.5 pmol/l), Δ4-androstenedione (3902, 3100, and 5618 pmol/l), 17 hydroxyprogesterone (1186, 1350, and 2397.5 pmol/l), and progesterone (1150, 1150, and 2950 pmol/l). We observed a significant increase in oestradiol (4638, 7864.5, and 1282 pmol/l) and Δ4-androstenedione (5932, 11 850, and 7477 pmol/l) (IVF, ICSI, and IUI respectively). The 48 h increase was significantly different between control and AMP for estradiol (1.5-fold for IIU, 1.8-fold for IVF, and 1.9-fold for ICSI) and Δ4-androstenedione (1.02-fold for IIU and 1.31-fold for ICSI). Testosterone, hydroxyprogesterone, and progesterone increase significantly only in the induced group, i.e. 1702.5 and 1470 pmol/l; 12 344 and 8650 pmol/l; and 2450 and 4150 pmol/l for IVF and ICSI respectively. There was no difference in the 48 h increase of those steroids between ICSI and FIV except for Δ4-androstenedione which increased (1.15-fold for FIV and 1.31-fold for ICSI).
Conclusion
rFSH treatment in AMP is likely to induce a biochemical ovarian hyperplasia. However, we have highlighted individual variations, which we are exploring by mass spectrometry.

DOI: 10.1530/endoabs.37.EP154

EP155

Lower peripheral fat persists in HIV-infected subjects despite viral suppression in the era of highly-active antiretroviral therapy

Louie Mar Gangcuangco[1,2], Jennifer Wong[2], Dominic Chow[2] & Cecilia Shikuma[2]
[1]Bridgeport Hospital–Yale New Haven Health, Bridgeport, Connecticut, USA; [2]University of Hawaii, Honolulu, Hawaii, USA.

Background
We compared body composition parameters in older HIV-positive individuals on stable antiretroviral therapy to age-matched HIV-seronegative individuals to assess whether differences in body composition parameters persist in the era of potent antiretroviral therapy.
Methods
Inclusion criteria to the ageing HIV cohort required subjects to be >40 years old and be on stable antiretroviral therapy for >6 months. Only subjects with undetectable plasma HIV RNA (<50 copies/ml) were included to eliminate the effects of uncontrolled HIV disease. Weight and height were measured in triplicate and averaged. Body composition (total fat, trunk fat, peripheral fat, lean tissue, and bone mineral content) was measured by dual-energy X-ray absorptiometry (DXA) using Lunar Prodigy scanner (GE Medical Systems, Inc., Milwaukee, WI, USA). Statistical analyses utilised were Wilcoxon's rank-sum test, χ^2 test, and multivariate linear regression.
Results
Body composition parameters from 133 HIV-positive individuals were compared to 74 HIV-seronegative controls. HIV-positive individuals were younger than HIV-seronegatives (medians: 51 years vs 54 years, $P=0.04$), and comprised of more males (88% vs 80%, $P<0.001$). Among HIV-positive individuals, the median CD4 count was 510 cells/μl. HIV-positive individuals had similar BMI (25.9 kg/m^2 vs 26.8 kg/m^2, $P=0.25$), but lower total fat (medians: 20.168 g vs 24.817 g, $P=0.005$) which was accounted for by differences in peripheral fat (6.811 g vs 9.634 g, $P<0.001$) with similar truncal fat levels. In a multivariate linear regression model, HIV status was a significant risk factor for lower peripheral fat content, adjusting for age, gender, ethnicity (Caucasian or non-Caucasian), BMI and past use of zidovudine or stavudine ($\beta = -0.08$, $P=0.02$).
Conclusion
Infection with HIV is still characterized by differences in body composition despite use of potent antiretroviral therapy. Specifically, HIV is associated with lower peripheral fat content independent of past use of antiretroviral therapy known to cause peripheral fat loss.
Disclosure
This work was supported by NIH grants R01HL095135 (C Shikuma) and U54RR026136 (J Hedges).

DOI: 10.1530/endoabs.37.EP155

EP156

An audit of prevalence and management of erectile dysfunction and LUTS in a diabetes clinic?

Anna Haley & Parijat De
Department of Diabetes and Endocrinology, City Hospital, Birmingham, UK.

Introduction
UK NICE guidelines recommend that men with diabetes mellitus (DM) should be reviewed annually regarding symptoms of erectile dysfunction (ED) in view of

possible phosphodiesterase-5 (PDE-5) inhibitor treatment. Previous studies have shown that 70% of men with ED have concomitant lower urinary tract symptoms (LUTS). It has been suggested that there may be some common patho-physiology accounting for the improvement in LUTS seen in men with ED and LUTS treated with PDE-5 inhibitors.

Aims

Our primary aim was to assess the prevalence and management of erectile dysfunction and concomitant LUTS in a diabetic cohort. Male patients attending a diabetic clinic in SWBH, Birmingham were consented to answer questions regarding their erectile function (IIEF) and urinary storage and voiding problems (IPSS).

Results

60 men (mean age 64 years) answered the questions (July–Oct 14). 53% reported moderate ($n=27$) or severe ($n=5$) LUTS. The most commonly reported symptoms were urgency, frequency, and weak stream. Nine men said they had no partner or no opportunity for sexual activity. Of those that did have a partner ($n=51$), 78% ($n=40$) reported symptoms of erectile dysfunction (IIEF score <25). Prevalence of moderate/severe LUTS in patients wishing to be sexually active but suffering from ED was 58% ($n=23$) vs 27% ($n=3$) in those with normal erections. Only six patients were already taking PDE-inhibitors.

Discussion

This survey has shown that of men with diabetes managed in a hospital clinic and who have partners ($n=51$), 70% ($n=36$) have symptoms of erectile dysfunction and aren't on any medication for this. Of these men, 61% ($n=23$) have concomitant LUTS. Overall a high proportion of men seen in a hospital diabetes clinic (presumably more complicated diabetic patients) had erectile dysfunction and urinary symptoms. These patients would potentially benefit from consideration for PDE-5 inhibitor treatment in the secondary care setting.

DOI: 10.1530/endoabs.37.EP156

EP157

Maternal obesity in pregnant rats is associated to increased levels of oestradiol during early postnatal life and altered ovarian follicular development in the offspring

Aldo Reyes[1], Luisa Ramírez[1], Valery Ambrosetti[1], Marcelo Guerra[1], Daniela Álvarez[1], Sofía Olguín[1], Daniela Fernandois[2], Ramón Sotomayor-Zárate[3] & Gonzalo Cruz[1]
[1]Laboratorio de Alteraciones Reproductivas y Metabólicas, CNPC, Facultad de Ciencias, Instituto de Fisiología, Universidad de Valparaíso, Valparaíso/Valparaíso, Chile; [2]Programa de Doctorado en Farmacología, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Santiago/Santiago, Chile; [3]Laboratorio de Neuroquímica y Neurofarmacología, CNPC, Facultad de Ciencias, Instituto de Fisiología, Universidad de Valparaíso, Valparaíso/Valparaíso, Chile.

Obesity during gestation has been related to predisposition to endocrine and metabolic diseases in the offspring. Regarding reproductive effects, an increase in BMI in pregnant mothers is associated with precocious puberty in their offspring. This has been replicated in animal models of high fat diet (HFD) administration to mothers. Also, gestational obesity has been associated to higher susceptibility to developing breast cancer in the offspring. As both precocious puberty and breast cancer are strongly related to higher oestrogens levels, we studied if offspring of rats exposed to a HFD had increased levels of endogenous oestradiol from neonatal until adult age. In addition, we evaluated ovarian follicular development in adult rats because early exposure to oestrogens alters ovarian follicular development. Twenty-four Sprague–Dawley rats were fed with HFD (60% kcal fat, Research Diet) and control diet (12% kcal fat, Champion) 1 month previous to pregnancy, during pregnancy and during nursing. Offspring rats were killed at postnatal day (PND) 1, PND7, PND14, PND30, and PND60. We found that offspring of obese mothers had an increase in body weight from PND1 until PND60, and they had an early vaginal opening indicating precocious puberty. At PND60 the offspring of obese mothers showed less antral follicles and appearance of follicular cyst in the ovary. Female offspring of obese mothers had an increase in serum levels of oestradiol at PND1, PND7, PND14, PND30, and PND60. We also found a decrease in the expression of hepatic cyp3a in offspring of obese mothers in concordance with clear signs of hepatic steatosis. We conclude that maternal obesity alters hepatic metabolism of oestradiol in the offspring leading to increased levels of endogenous oestradiol. In addition, the increase in oestradiol levels during early postnatal development may be responsible of altered reproductive function in the offspring of obese mothers.

Disclosure

FONDECYT grant number 11130707.

DOI: 10.1530/endoabs.37.EP157

EP158

Glucagon-like peptide-1 stimulates insulin secretion and then somatostatin secretion in rat islets

Seungjoon Oh[1,2], So Young Park[2], Kwang Sik Suh[2] & Sung-Woon Kim[1,2]
[1]Endocrinology, School of Medicine, Kyung Hee University, Seoul, Republic of Korea; [2]Endocrinology, Medical Hospital, Kyung Hee University, Seoul, Republic of Korea.

Glucagon-like peptide-1 (GLP-1) is known to stimulate insulin and somatostatin secretion in pancreatic islet cells. The exogenous somatostatin inhibits insulin secretion, but GLP-1 increases insulin secretion in spite of stimulating somatostatin secretion from δ-cell. So, we investigated whether there exists a time difference of insulin and somatostatin secretion inside the islets after GLP-1 stimulation or insulin secretion depends on secreted GLP-1 or somatostatin concentration inside the islets. We isolated pancreatic islets from five 8-week-old Sprague–Dawley rats by collagenase digestion. The islets were incubated in RPMI-1640 medium before experiments. *In vitro*, insulin and somatostatin measured at 5, 10, and 30 min depending on glucose (2.7, 5.5, and 16.7 mM as hypo-, normo-, and hyperglycaemic condition respectively) and GLP-1 concentrations (0, 0.1, and 10 ng/ml) from culture media using ELISA kit. Each well contained 30 islets/well. Insulin secretion showed continuously increased by time and GLP-1 concentration at any glucose concentration. Somatostatin secretion was increased significantly 10 min later after GLP-1 administration at hypo- and normoglycaemia. However, in hyperglycaemia, insulin secretion showed the same pattern compared with the other glycaemic conditions, but somatostatin was maximally stimulated until 10 min and decreased after that without GLP-1 administration. Adding the GLP-1, somatostatin was increased continuously until 30 min. This suggested hyperglycaemic condition itself might need more insulin secretion in the β-cell than somatostatin secretion in δ-cell. Therefore, we observed time lag of intraislet somatostatin secretion was existed with GLP-1 stimulation. We observed GLP-1 induced insulin secretion is noted earlier in β-cell than somatostatin secretion in δ-cell of rat islets. Hyperglycaemic condition might primarily secrete insulin even though and inhibit somatostatin secretion inside the islets.

DOI: 10.1530/endoabs.37.EP158

EP159

Treatment with antifungal agents, fenhexamid and cyprodinil, resulted in an increase of cell cycle- and metastasis-related genes in an oestrogen receptor-dependent pathway in cellular and xenografted mouse models with BG-1 ovarian cancer cells

Ryeo-Eun Go & Kyung-Chul Choi
Laboratory of Biochemistry and Immunology, College of Veterinary Medicine, Chungbuk National University, Cheongju, Chungbuk, Republic of Korea.

Fenhexamid and cyprodinil are antifungal agents used in agricultural applications and present at measurable amounts in fruits and vegetables. In this study, the effects of fenhexamid and cyprodinil on cancer cell viability and metastasis were examined and the expression levels of proteins such as cyclins D1 and E, and cathepsins B and D were analysed in BG-1 ovarian cancer cells with oestrogen receptors (ERs). BG-1 cells were cultured with 0.1% DMSO (control), 17β-oestradiol (E_2; 1×10^{-9} M), fenhexamid or cyprodinil (10^{-5}–10^{-8} M). As results, in MTT assay, E_2 as a positive control markedly increased BG-1 cell viability about five times and these antifungal agents increased BG-1 cell viability about 1.5–2 times compared to control. When the respective treatment was co-treated with ICI 182 780, an ER antagonist, BG-1 cell viability was reversed to the level of control. In wound-healing scratch assay, the scratched area was reduced by BG-1 cells treated with E_2 or these antifungal agents compared with control. However, when BG-1 cells were treated with ICI 182 780, the scratched area was maintained to the level of control. Protein levels of cyclins D1 and E, cathepsins B and D were induced by E_2 and these antifungal agents, but when co-treated with ICI 182 780, the increased protein levels were reversed. In xenografted mouse models transplanted with BG-1 cells, E_2 significantly increased the tumour mass formation about six times and cyprodinil also induced tumor formation about two times compared to vehicle (0.1% DMSO) during 80 days. However, fenhexamid did not increase the tumour mass formation. These results imply that the fenhexamid and cyprodinil may have disruptive effects on ER expressing cancer by alteration of cell cycle- and metastasis-related genes via ER dependent pathway. This work was supported by Basic Science Research

Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (MEST) of the Republic of Korea (2014R1A1A2055295).
Disclosure
This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (MEST) of the Republic of Korea (2014R1A1A2055295).
DOI: 10.1530/endoabs.37.EP159

EP160

Ovarian cancer growth was induced by 2,3,7,8-tetrachlorodibenzo-*ρ*-dioxin through the regulation of *CYP1A1* gene in an oestrogen receptor-dependent pathway in BG-1 ovarian cancer cells

Ryeo-Eun Go & Kyung-Chul Choi
Laboratory of Biochemistry and Immunology, College of Veterinary Medicine, Chungbuk National University, Cheongju, Chungbuk, Republic of Korea.

Environmental factors such as high meat consumption, caffeine, cigarette smoking, and endocrine disrupting chemical (EDCs) may enhance the risk of ovarian cancer. Cytochrome P450 (CYP) 1A1 may play a major role in metabolic activation of procarcinogens to carcinogens. 2,3,7,8-Tetrachlorodibenzo-*ρ*-dioxin (TCDD) is a commonplace pollutant and a promoter of carcinogenesis as the most potent substance. In this study, we examined the effects of TCDD in the presence of 17β-estradiol (E_2) on the expressions of CYP1A1, CYP1B1, and aryl hydrocarbon receptor (AhR) by RT-PCR and western blot analysis. In addition, the cell viability by TCDD and E_2 was examined in BG-1 human ovarian cancer cells by MTT assay. To evaluate the cell viability, BG-1 cells were cultured with control (0.1% DMSO), E_2 (1×10^{-9} M), or TCDD (10^{-6}–10^{-8} M). E_2 markedly increased BG-1 cell viability about five times and TCDD also induced BG-1 cell viability the most at 1×10^{-8} M compared to control. When co-treated with ICI 182 780, an ER antagonist, BG-1 cell viability was reversed to the level of control. Although, mRNA expression of CYP1B1 or AhR was not altered by E_2 or TCDD, the transcriptional level of CYP1A1 appeared to be increased by E_2 or TCDD in a time-dependent manner. Furthermore the translational level of AhR and CYP1A1 appeared to be increased by E_2 or TCDD in a time-dependent manner. In xenografted mouse models transplanted with BG-1 cells, E_2 treatment significantly increased the tumour mass formation about six times and TCDD induced tumour formation about four times compared to vehicle (0.1% DMSO) during 80 days. In addition, expression levels of proliferation cell nuclear antigen, AhR and CYP1A1 are increased in E_2 or TCDD-treated tumour section compared to the control. Taken together, TCDD may induce ovarian cancer cell growth via *CYP1A1* gene expression and have a disruptive effect in ER expressing cells or tissues. This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (MEST) of the Republic of Korea (2014R1A1A2055295).
Disclosure
This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (MEST) of the Republic of Korea (2014R1A1A2055295).

DOI: 10.1530/endoabs.37.EP160

EP161

Hormonal disorders in adult women with acne

Liudmyla Naumova
Bogomolets National Medical University, Kyiv, Ukraine.

Introduction
Up to 30% of women of reproductive age suffer from acne. In most cases, acne leads to different reproductive disorders.
The purpose of the study
To determine the frequency of hormonal disorders in women with acne and acne-similar changes of the skin.
Methods and materials of research
The study involved 30 female patients of 18–55 years old. Examined were their stature, the spread of acne and its predominant localization, and the presence of hirsutism syndrome. Among morphometric parameters measured were the circumference of waist and hips with calculation of the waist:hip ratio. BMI was determined as well. All patients were tested for venous blood glucose and HbA1c. Hormonal examination included the determination of following parameters: free testosterone, prolactin, TSH, 17-oxyprogesterone, DHEAS, oestrogen, progesterone, steroid-binding globulin, and anti-Müllerian hormone. Sonography of thyroid gland and pelvic organs was also performed.
Results of the survey
Study women were found to have ovarian hyperandrogenism, among different pathological conditions related to acne and acne-similar rash with the following percentage: atypical (late) forms of congenital adrenal dysfunction (27%); polycystic ovarian syndrome (20%); type 2 diabetes mellitus (17%); hypothyroidism (12%); hyperprolactinaemia (12%); early menopause (10%); and adrenal hyperandrogenism (1%). These parameters were only normal in 1% of examined subjects.
Conclusions
The background of acne and acne-similar rash changes in women of reproductive age are numerous hormonal and metabolic changes in the female organism. Not all cases of acne are accompanied with hyperandrogenism. Local treatment of acne in women should be preceded by intensive hormonal and instrumental examination of woman's reproductive system, and determination of carbohydrate metabolism and thyroid status.

DOI: 10.1530/endoabs.37.EP161

EP162

Modulation of the circadian clock by glucocorticoid receptor in H295R cell line

Zsolt Nagy[1,2], Henriett Butz[3], Istvan Liko[2], Karoly Racz[1,3] & Attila Patocs[2,4]
[1]2nd Department of Medicine, Faculty of Medicine, Semmelweis University, Budapest, Hungary; [2]'Lendulet' Hereditary Endocrine Tumors Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest, Hungary; [3]Molecular Medicine Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest, Hungary; [4]Department of Laboratory Medicine Institute, Faculty of Medicine, Semmelweis University, Budapest, Hungary.

Background
Peripheral clocks are set by different nervous, hormonal and metabolic stimuli and regulate the circadian expression of several genes. It has been demonstrated that circadian oscillation of gene expression can be detected in various cell lines *in vitro*.
Aim
To explore whether a peripheral clock could be induced in human adrenocortical cell line H295R and what are the effects of glucocorticoids on this clock system.
Methods
H295R human adrenocortical cell line was studied. For serum shock experiments cells were serum starved for 24 h and incubated with 30% Nu serum for 2 h then returned to normal medium with either vehicle or 100 nmol dexamethasone (Dex). For Dex experiments cells were serum starved for 24 h, maintained in serum free medium and treated with vehicle or 100 nmol Dex with or without 1 μmol RU486. Cells were harvested at the indicated time points. All experiments were carried out in triplicate. RT-PCR was carried out using predesigned TaqMan gene expression assays. PER1, PER2, CRY1, ARNTL, NR1D1, NR3C1, StAR, POMC, CRH, and actin expressions were measured by qRT-PCR on 7500 Fast Real-Time PCR System.
Results
After synchronisation of cells the rhythmic oscillation of clock genes *PER1, PER2, NR1D1*, and *ARNTL* was observed. Glucocorticoid treatment induced a rapid respond of PER1 in a glucocorticoid receptor (GR)-dependent manner. Continuous glucocorticoid stimulation caused elevation of PER1 and altered its rhythm. Glucocorticoid treatment induced the expression of PER2 and delayed its phase, increased expression of CRY1 and, after 6 h, it suppressed expression of NR1D1. Administration of a GR antagonist, RU486 disrupted the circadian oscillation of clock genes and prevented the acute changes in PER1, PER2 and CRY1 levels. These alterations occurred independently from ACTH or CRH.
Conclusions
Our data demonstrated that a peripheral clock system is present in human adrenocortical cell line and periodic oscillation of clock genes are influenced by glucocorticoids.

Disclosure
The authors received financial support from Hungarian Scientific Research Fund (OTKA PD-100648) and National Development Agency (KTIA-AIK-10_2012-0010).

DOI: 10.1530/endoabs.37.EP162

EP163

An information theoretic approach to GnRH signalling

Kathryn Garner[1], Rebecca Perrett[1], Margaritis Voliotis[2], Thanh Pham[3], Krasimira Tsaneva-Atanasova[4] & Craig McArdle[1]
[1]Laboratories for Integrative Neuroscience and Endocrinology, School of Clinical Sciences, University of Bristol, Bristol, UK; [2]School of Mathematics, University of Bristol, Bristol, UK; [3]Texas A&M University, College Station, Texas, USA; [4]Department of Mathematics, College of Engineering, Mathematics and Physical Sciences, University of Exeter, Exeter, UK.

One way in which cells receive information about their environment is through hormones binding to appropriate receptors on their cell surface. Single cell measurements of signalling proteins typically reveal high cell–cell variability raising questions about how reliably individual cells sense their environment in order to make decisions. Information theoretic approaches can be used to explore such sensing, treating cell signalling pathways as 'noisy' communication channels. Mutual information (MI) can be calculated between system inputs and outputs as a statistical measure of the reliability of sensing. GnRH acts via $G_{q/11}$-coupled seven-transmembrane receptors to stimulate ERK and nuclear factor of activated T-cells (NFAT), but information transfer has not previously been quantified for these (or other) hormone receptors. Here, we do so using automated fluorescence microscopy to quantify dual-phosphorylated (pp)ERK and the nuclear fraction (NF) of NFAT1c–EFP as activation readouts. In gonadotroph-derived LβT2 cells, GnRH increased ppERK and NFAT-NF levels with maximal effects at 5–60 min. MI between GnRH and ppERK or between GnRH and NFAT-NF followed similar time courses but did not exceed 0.8 bits, implying that information transfer through these pathways is insufficient for an individual cell to unambiguously distinguish even two states of the environment. We also used imaging reporters for transcription activation (Egr1-driven or NFAT-RE-driven asRED) and again MI between GnRH and these outputs was always <0.8 bits. As a possible explanation for such unreliable sensing we consider GnRH receptor (R) number, using recombinant adenovirus to express GnRHR at sub-physiological to super-physiological levels ($<20\,000$–$>170\,000$ sites/cell) in HeLa cells. This revealed that information transfer is indeed dependent on GnRHR number but MI values were <0.8, even at the highest GnRHR levels. Accordingly, this novel approach to quantification of information transfer suggests that individual pathways and cells are very inefficient sensors of GnRH concentration.

Disclosure
This work was supported by the Biochemical and Biophysical Science Research Council (BBSRC grant number BB/J014699/1).

DOI: 10.1530/endoabs.37.EP163

EP164

Prevalence of vitamin D deficiency in Slovak women with polycystic ovary syndrome and its relation to metabolic and reproductive abnormalities

Jana Figurová[1], Ingrid Dravecká[1], Martin Javorský[2], Jana Petríková[1] & Ivica Lazúrová[1]
[1]1st Department of Internal Medicine, Medical Faculty, P.J.Šafarik University, Košice, Slovakia; [2]4th Department of Internal Medicine, Medical Faculty, P.J.Šafarik University, Košice, Slovakia.

Objective
Polycystic ovary syndrome (PCOS) is the most common endocrine disorder characterised by menstrual dysfunction, infertility, presence of polycystic ovaries and biochemical and clinical hyperandrogenism affecting up to 4–18% women of reproductive age. Vitamin D is thought to influence the development of PCOS through gene transcription and hormonal modulation of insulin metabolism and fertility regulation. The aim of this prospective case–control study was to investigate prevalence of vitamin D deficiency and its relation to clinical, anthropometrical, and biochemical findings in PCOS and controls.
Methods
25(OH)D, anthropometric, endocrine, and metabolic parameters were evaluated in 99 women with PCOS according to Rotterdam criteria and in 66 controls, recruited prospectively.
Results
There was no significant difference in 25(OH)D levels between PCOS women and controls (24.79 ± 10.77 ng/ml vs 25.07 ± 10.14 ng/ml, $P=0.868$) and also in the prevalence of 25(OH)D deficiency in both groups (80% vs 70%; $P=0.138$). PCOS women with metabolic syndrome (MS) had lower serum 25(OH)D compared to those without MS (20.6 ± 8.3 ng/ml vs 25.9 ± 11.3 ng/ml, $P=0.049$). PCOS women with vitamin D deficiency had borderline higher serum triacylglycerides (1.44 ± 0.93 vs 1.03 ± 0.46, $P=0.051$) and tended to have higher HOMA-IR (median (quartiles): 2.24 (1.38–3.51) vs 1.85 (1.04–3.68), $P=0.467$) compared to PCOS with sufficient vitamin D levels. 25(OH)D correlated positively with HDL-cholesterol in all subjects ($r=0.159$, $P=0.043$; P adjusted for age, BMI, $P\_adj=0.03$) and negatively with LH/FSH ratio ($r=-0.211$, $P=0.037$) in PCOS.
Conclusions
Insulin resistance and other metabolic abnormalities in PCOS women seem to be related to PCOS rather than to vitamin D deficiency.

DOI: 10.1530/endoabs.37.EP164

EP165

Identification of p53 regulation site on the p27 promoter

Sung-Po Hsu[1,2], Po-Han Lin[2] & Wen-Sen Lee[1,2]
[1]Department of Physiology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; [2]College of Medicine, Graduate Institute of Medical Sciences, Taipei Medical University, Taipei, Taiwan.

Angiogenesis is a crucial physiological phenomenon in female reproductive cycle. Our previous studies have shown that progesterone could inhibit proliferation of human umbilical vein endothelial cells (HUVEC) through a p53-dependent mechanism, by which the levels of p21 and p27 protein were increased, subsequently inhibiting the CDK2 kinase activity, and finally impaired the transition of the cell from the G1 phase to the S phase. While previous studies had clearly demonstrated that p53 protein directly activates p21 expression though binding onto the p21 promoter, the p53-regulated p27 gene expression has not been reported. Accordingly, the aim of this research was to investigate the precise binding domains of p53 protein on the p27 promoter. Luciferase assay showed that the potential p53 binding region spans on sites 258–310 upstream the start codon of the p27 gene. Within this range, there are three potential binding fragments with 70% similarity of p53 consensus binding domain and between each fragment is separated by <13 bp. Deletion or TCCT sequence replacement at the internal site of anyone of these fragments resulted in an irresponsiveness to progesterone treatment, suggesting that all these three fragments are essential for p53 protein to regulate the p27 promoter activity. Moreover, immunoprecipitation and chromatin-immunoprecipitation analysis demonstrated that both the formation of p53-progesterone receptor complex in the nucleus and the binding of progesterone receptor onto the p53 binding fragment of the p27 promoter were increased by progesterone treatment, suggesting that progesterone receptor might be also involved in the p53-regulated the p27 promoter activity. To our knowledge, this is the first demonstration that progesterone up-regulated p27 expression in HUVEC through a p53-dependent pathway.

Disclosure
This work was supported by grant from NSC 100–2320-B-038-011 to Dr W-S Lee and grant from NSC 102-2320-B-038-023 and TMU101-AE1-B45 to Dr S-P Hsu.

DOI: 10.1530/endoabs.37.EP165

EP166

The influence of late onset hypogonadism on the formation of proinflammatory cytokines imbalance in patients with obesity and type 2 diabetes

Irina Khripun, Zalina Gusova, Elizaveta Dzantieva, Valentina Puzireva, Asiat Sultanmuradova & Sergey Vorobiev
Rostov State Medical University, Rostov-on-Don, Russia.

Currently actively studied the role of certain inflammatory and proinflammatory cytokines in the pathogenesis of insulin resistance, type 2 diabetes, obesity, atherosclerosis. However, the influence of testosterone deficiency on the balance of proinflammatory cytokines is unexplored. The aim of the work was to evaluate the influence of testosterone deficiency on metabolic parameters and levels of proinflammatory cytokines in patients with obesity and type 2 diabetes.

Materials and methods

We examined the 85 male patients, aged 40–65 years with obesity and type 2 diabetes, which were divided into two groups, matched for age. The first group included 44 patients with testosterone levels above 12.1 nM/l, the second – 41 men with content of hormone <12.1 nM/l.

Results and discussion

Analysis of the data shows a statistically more significant BMI in the group of hypogonadal patients (BMI 42.03 ± 1.44 kg/m^2), compared with eugonadal males (BMI 34.36 ± 1.22 kg/m^2). Also in the second group there were a statistically significant increases in the levels of serum total cholesterol (6.64 ± 0.13 vs 5.79 ± 0.16 mM/l) and triglycerides (2.31 ± 0.31 vs 1.72 ± 0.17 mM/l). In estimating the concentration of TNF-a in the serum was found that its level in patients with deficiency of testosterone (6.32 ± 0.49 pg/ml) was significantly higher ($P \leq 0.05$) that those without hypogonadism (4.38 ± 0.37 pg/ml). The results of the study of IL-6 showed a statistically significant increase in its content in the serum of patients with hypogonadism (5.39 ± 0.89 pg/ml) compared with patients with normal levels of testosterone (3.78 ± 0.36 pg/ml).

Conclusion

Reduced serum testosterone level is a factor contributing to manifestations of metabolic disorders and cytokine imbalance in patients with obesity and type 2 diabetes. Androgen deficiency may be regarded as an additional risk factor for cardiovascular disease and diabetes.

Disclosure

This work was supported by the Russian Science Foundation, grant No. 14-25-00052

DOI: 10.1530/endoabs.37.EP166

EP167

Palmitic acid enhances TLR4 expression and promotes resistin/TLR4 signalling

Hamza Amine[1,2], Yacir Benomar[1,2], Arieh Gertler[3] & Mohammed Taouis[1,2]
[1]Neuroendocrinologie Moléculaire de la Prise Alimentaire, University of Paris-Sud, UMR 9197, Orsay, France; [2]Neuroendocrinologie Moléculaire de la Prise Alimentaire, Neuroscience Paris Saclay Institute, CNRS UMR 9197, Orsay, France; [3]Faculty of Agricultural, Food and Environmental Quality Sciences, The Institute of Biochemistry, Food Science, and Nutrition, The Hebrew University of Jerusalem, Rehovot, Israel.

Toll-like receptor 4 (TLR4) has a critical role in innate immunity, and the activation of inflammatory pathways plays an important role in the induction of insulin resistance. Indeed, we have recently demonstrated that TLR4 is implicated in resistin-induced inflammation and insulin resistance in the hypothalamus.[1] We have also shown that TLR4 is up-regulated in the hypothalamus of mice fed a high-fat diet. Here, we aim to decipher the molecular mechanisms implicated in the regulation of TLR4 expression. For this purpose, human neuroblastoma cells (SHSY-5Y) were exposed during 4 h to either palmitic acid (a saturated fatty acid) or the omega-3 polyunsaturated fatty acid docosahexaenoic acid (DHA). Cells were then treated with resistin. Firstly we analysed the effect of resistin, palmitic acid and DHA on inflammation markers. We show that only resistin was able to activate NF-κB and to increase the phosphorylation of Akt and p38 MAPK. However, palmitic acid pretreatment increases the expression of inflammatory cytokines (IL-6 and TNF-α), similar to resistin. Interestingly, DHA pretreatment suppresses palmitic acid and resistin induced up-regulation of IL-6 and TNF-α. Secondly, we studied the possible synergistic interaction between resistin and palmitic acid on TLR-4 expression. We show that palmitic acid pretreatment increases TLR4 expression, at both protein and mRNA levels, while DHA pretreatment had no effect. Importantly, palmitic acid pretreatment potentiates resistin effects. In conclusion, we show for the first time, to our knowledge, that palmitic acid induces TLR4 expression and this leads to the amplification of resistin effects promoting then insulin resistance at the neuronal level.

Reference

1. Benomar *et al*., Diabetes. 2013 **62** 102–14.

Disclosure

This work was supported by funds from University of Paris Sud and the CNRS (Centre National de la Recherche Scientifique, France).

DOI: 10.1530/endoabs.37.EP167

EP168

Heterogeneity of human chorionic gonadotropin (hCG) in commercial preparations of hCG and human menopausal gonadotropin

Laura Riccetti[1], Elisa Pignatti[1,2] & Manuela Simoni[1,3]
[1]Unit of Endocrinology, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy; [2]Center for Genomic Research, University of Modena and Reggio Emilia, Modena, Italy; [3]Azienda USL of Modena, Modena, Italy.

Introduction

Human chorionic gonadotropin (hCG) is a glycoprotein hormone composed by two subunits, an alpha subunit common to all gonadotropins and a specific beta subunit. hCG is produced by trophoblast cells as differently glycosylated isoforms with a wide range of molecular weight, from 30 to 50 KDa ('regular' hCG is 37 KDa). hCG is used in the treatment of infertility. The aim of this study is to analyse and compare the composition of different commercial hCG.

Design

Three hCG preparations from pregnancy urine (50 mIU Gonasi-IBSA, 50 mIU Pregnyl-Organon, 70 mIU Sigma C0434), one recombinant (5 ng r-hCG, Ovidrel-Serono) and an urinary hMG (75–300 mIU Meropur-Ferring) were compared by 12% SDS–PAGE and western blotting using a polyclonal antibody against hCG beta subunit (Dako A0231). Different conditions were used in processing all the preparations such as denaturing and reducing samples or preserving their 'native' conformation. The western blotting patterns were confirmed by ConA Affinity Chromatography.

Results

Despite no particular differences were observed under denaturing-reducing conditions, we found qualitatively and quantitatively peculiar patterns under 'native' conditions. In the urinary hCG preparations up to three isoforms were found with different molecular weights (32, 37 and 45 KDa; $n=4$). In contrast, in r-hCG four variants were found (one doublet at 31–32 KDa and a doublet more expressed at 44–45 KDa; $n=4$). All preparations, including hMG, seem to contain hyperglycosylated hCG (hCG-H) of about 45 KDa which was characterized against hCG-H purified from human choriocarcinoma cell line (JEG-3) culture medium as control. ConA Affinity Chromatography confirmed that all the isoforms detected were glycosylation variants of hCG.

Conclusions

The commercial hCG and hMG preparations consist of several isoforms which differ in molecular weight and grade of glycosylation. Surprisingly, r-hCG has a wider range of glycosylated variants than urinary hCG. The peculiar signal pattern observed by western blotting demonstrates the heterogeneity of hCG in commercial preparations.

DOI: 10.1530/endoabs.37.EP168

EP169

Differential cell cycle control protein profiles characterise bronchial carcinoids sensitive to mTOR inhibitors

Katiuscia Benfini, Teresa Gagliano, Erica Gentilin, Eleonora Riva, Simona Falletta, Carmelina Di Pasquale, Marta Bondanelli, Maria Rosaria Ambrosio, Ettore Ciro degli Uberti & Maria Chiara Zatelli
Section of Endocrinology and internal medicine, Department of Medical Sciences, University of Ferrara, Ferrara, Italy.

Background

Bronchial carcinoids (BC) are rare neoplasm, still orphan of medical therapy, which arise from neuroendocrine cells. It has been previously demonstrated that the atypical BC human cell line NCI-H720 is sensitive to everolimus (E), an m-TOR inhibitor, in terms of cell viability reduction, with a G0 cell-cycle arrest and a Cyclin D1 protein reduction. On the contrary, the typical human BC cell line NCI-H727 is not sensitive to E, despite the Cyclin D1 reduction. The mechanisms underlying this phenomenon have not been fully clarified, yet.

Aim
Our aim is to further investigate cell cycle mechanisms that underlie resistance to mTOR inhibitors in BC cells, in order to identify new therapeutic approaches.
Materials and methods
Human BC cell line cultures (NCI-H720 and NCI-H727 cells) were investigated by Western blot, cell viability and caspase activation assays before and after a challenge with E.
Results
Protein profiling of the main complexes regulating G0/G1 ≫ S progression (CDK2/Cyclin E and CDK4/Cyclin D1) and CDK-inhibitors (p27 and phospho p27_SER10) was performed. At basal levels the two BC cell lines showed a different protein profile with the positive regulators of the cell cycle (Cyclin D/CDK4 and Cylin E/CDK2) more expressed in NCI-H727 cells (resistant to E) as compared to NCI-H720 cells (sensitive to E), suggesting that in the Resistant BC cell line p27kip1, despite being over-expressed, has an impaired function. We also found that E reduced Cyclin D/CDK4 protein complex as well and Cyclin E expression, but induced CDK2 expression, possibly explaining the escape of NCI-H727 from the antiproliferative effects of E. On the other hand, no modification of cell cycle control protein profile has been observed in NCI-H720 after treatment with E, indicating that the latter exerts its antiproliferative effects on this cell line by a cyclin-independent mechanism.
Conclusion
Our data indicate that resistance to mTOR inhibitors may be linked to a deranged cell cycle control protein profile. Therefore the characterization of these proteins may represent a putative marker of resistance to E, possibly contributing to a better patients selection for a therapeutic approach with mTOR inhibitors.

DOI: 10.1530/endoabs.37.EP169

EP170

Influence of mTOR and ERK 1/2 pathways on the IGF1 negative feedback in GH secreting pituitary adenoma cell line

Carmelina Di Pasquale[1], Mariaenrica Bellio[1], Erica Gentilin[1,2], Teresa Gagliano[1], Simona Falletta[1], Katiuscia Benfini[1], Maria Rosaria Ambrosio[1], Ettore degli Uberti[1,2] & Maria Chiara Zatelli[1,2]
[1]Section of Endocrinology and Internal Medicine, Department of Medical Science, University of Ferrara, Italy, Ferrara, Italy; [2]LTTA, laboratorio per le tecnologie delle terapie avanzate, Ferrara, Italy.

Background
Gigantism and acromegaly are the main consequences of GH excess, mainly due to a pituitary adenoma. Surgery is the first therapeutic option, but also medical therapy is employed, being mostly represented by somatostatin analogues (SSA), that reduce both tumour mass and GH hypersecretion. However about 10% of patients is resistant to SSA.
PI3K/Akt/mTOR pathway, activated by growth-factors such as IGF1, is important in regulating many cellular processes.
Aim
To understand whether PI3K/Akt/mTOR and ERK 1/2 pathway can influence IGF1 feed-back in GH secreting pituitary adenoma cell lines, we employed three inhibitors: everolimus (mTOR inhibitor), NVP-BEZ235 (mTOR and PI3K inhibitor) and SCH772984 (ERK 1/2 inhibitor), evaluating their effects in presence or in absence of IGF1.
Materials and methods
Cell viability and GH secretion assays have been performed in the GH3 cell line (rat GH-secreting pituitary adenoma cell line).
Results
IGF1 induced cell viability by 30%. Everolimus significantly reduced viability up to 30%, and this effect was not counteracted by IGF1. NVP-BEZ235 reduced cell viability and IGF1 counteracted this effect, suggesting that this compound could act, at least in part, on IGF1 activated pathways. GH secretion was reduced by IGF1 (40%); Everolimus and NVP-BEZ235 did not significantly affect GH secretion and these compounds did not enhance the negative feed-back of IGF1 on GH secretion. SCH772984 did not influence viability but reduced GH secretion up to 20% without enhancing IGF1 negative feed-back. Moreover, Everolimus and NVP-BEZ235 did not influence SCH772984 effects.
Conclusions
These data indicate that IGF1 is important in regulating proliferation and GH secretion in GH3 cells. mTOR blockade reduce viability without affecting GH secretion. ERK 1/2 affects secretion but not IGF1 negative feed-back. In conclusion, our data suggest that mTOR and ERK 1/2 pathways are not involved in IGF1 feed-back on GH secretion.

DOI: 10.1530/endoabs.37.EP170

EP171

Role of TGFβ1 in pancreatic neuroendocrine tumour

Simona Falletta[1], Teresa Gagliano[1], Erica Gentilin[1], Carmelina Di Pasquale[1], Katiuscia Benfini[1], Vanessa Polenta[2], Massimo Falconi[2], Maria Rosaria Ambrosio[2], Stefano Partelli[2], Ettore degli Uberti[1] & Maria Chiara Zatelli[1]
[1]Section of Endocrinology and Internal Medicine, Department of Medical Science, University of Ferrara, Italy, Ferrara, Italy; [2]Pancreatic Surgery Unit, San Raffaele Hospital, Vita-Salute San Raffaele University, Via Olgettina 60, 20132 Milan, Italy.

Introduction
Neuroendocrine tumours (NETs) are heterogeneous neoplasms arising from neuroendocrine cells spread in the respiratory and gastro-entero-pancreatic epithelium. The role of transforming growth factor beta-1 (TGFβ1) in NET biology is largely unknown. TGFβ1 signalling pathway is tumour suppressive in most non-transformed epithelial cell lines. In contrast, many human carcinomas are refractory to the growth–inhibitory effects of TGFβ1.
Aim
To understand the possible role of TGFβ1 on cell viability and apoptosis in pNET and to evaluate whether this protein may affect the response to therapeutic molecules currently used in the management of pNETs.
Methods
20 pNETs primary cultures were treated with TGFβ1 and/or everolimus, a mTOR inhibitor. Cell viability and caspase activity were evaluated.
Results
TGFβ1 reduced cell viability and promoted apoptosis (∼50%) in four pNETs. In the same group, TGFβ1 enhanced (+15%) the growth arrest induced by everolimus alone (50%). On the contrary in 16 pNETs we observed a 30% increase in cell viability and a similar decrease in caspase activation.
Conclusions
In conclusion, TGFβ1 reduces cell viability in a pNET sub-group and may cooperate with everolimus. Further studies are necessary to understand TGFβ1 related functional context in pNETs.

DOI: 10.1530/endoabs.37.EP171

EP172

Reduction of growth and lesser utilisation of energy reserves in heroin addicted boys during pubertal development

Muhammad Saqlain[1], Ghazala Kaukab Raja[1], Maleeha Akram[2], Samar Minallah[2], Afzaal Ahmad[2], Mazhar Qayyum[2] & Shakeel Raza Rizvi[2]
[1]Department of Biochemistry Pir Mehr Ali Shah Arid Agriculture University Rawalpindi, Rawalpindi, Pakistan; [2]Department of Zoology Pir Mehr Ali Shah Arid Agriculture University Rawalpindi, Rawalpindi, Pakistan.

The secretion of leptin, an indicator of energy reserves, declines as energy stores are consumed in growth and development at puberty. The pubertal growth and development are often altered under different kinds of stresses. Usually, stress stimulates the release of cortisol, which is a labelled marker of stress. Early teens are inclined to drug abuse that may put their bodies under stress and may induce excessive secretion of cortisol. Since, sustained high levels of cortisol may affect growth rate at puberty, the present investigation examined body weight (BW), height, BMI and plasma concentrations of leptin and cortisol in non-smoking ($n=220$) and heroin addicted ($n=211$) boys and observed relationship between heroin addiction and circulating concentrations of leptin and cortisol during different stages of pubertal development. Data were analysed using Student's *t* test, ANOVA and Pearson correlation. The mean BW, height, BMI and plasma concentrations of cortisol progressively increased throughout puberty and adolescence in both non-smoking and heroin addicted boys. The concentrations of cortisol were significantly higher during all stages of pubertal development in heroin addicted boys compared to non-smoking boys. The concentrations of leptin gradually declined through puberty in both groups but still remained markedly higher in heroin addicted boys. In non-smoking boys, cortisol and leptin concentrations were negatively correlated with each other at puberty. A position relationship was observed between heroin addiction and concentrations of cortisol and leptin at different stages of pubertal development. At the age of 20 years, non-smoking boys were ∼10 kg heavier in weight and ∼5 cm taller in size than heroin addicted boys. In conclusion, this study demonstrates reduction in growth and partial utilization of energy reserves in heroin addicted boys compared to non-smoking boys, who appeared to utilize all their energy reserves in attaining full growth at puberty.

DOI: 10.1530/endoabs.37.EP172

EP173

Persistent Mullerian duct syndrome: a case report

Raquel Almeida, António Canha, Jorge Santos, Anabela Rocha & Jorge Dores
Centro Hospitalar do Porto, Porto, Portugal.

Persistent Mullerian duct syndrome (PMDS) is a rare disorder of sex development characterized by the persistence of Mullerian duct derivatives in a genotypic (46,XY) and phenotypic normally virilised male. PMDS is transmitted in an autosomal recessive manner, caused by mutations in the anti-Mullerian hormone gene or in the gene encoding the AMH receptor. The authors report a case of a male patient aged 62 years, with bipolar disorder, referred to the endocrinologist by incidental discovery of uterus and fallopian tubes during emergency laparotomy for acute peritonitis associated with Crohn's disease diagnosed later. In the anamnesis: childbirth at home in a village, appropriate pubertal development, no history of gynecomastia; no erectile dysfunction or changes in libido; had no children although there was that intention. At the physical exam: male phenotype with normal penis but missing testicles in the scrotum; not eunuchoid proportions; no gynecomastia; hairy distribution with male pattern and male voice. MRI showed 'uterus in middle location with normal anatomical pattern, inserted in the region of the seminal vesicles; prostate and seminal vesicles with normal characteristics; gonads in ovarian topography with uncharacteristic signal behavior for ovarian tissue, suggesting ovotestes'. Hormonal study revealed hypergonadotrophic hypogonadism and no other abnormalities; Normal karyotype 46,XY. Normal bone densitometry. Histology of the right gonad (the patient refused removal of both gonads) showed atrophic testicular tissue with scattered microcalcifications, without signs of malignancy. The authors decided to present this case not only because of its rarity, but also to draw attention to the late diagnosis that was performed despite the presence of cryptorchidism. Early diagnosis and treatment of PMDS can reduce the risk of degeneration and testicular malignancy associated with prolonged cryptorchidism. Surgical replacement of the gonads in the scrotum does not ensure fertility if there is an abnormal connection between the testicles and the excretory ducts.

DOI: 10.1530/endoabs.37.EP173

EP174

47,XYY syndrome and hypogonadotropic hypogonadism: is this coincidence or a diverse spectrum of the syndrome?

Fatma Dilek Dellal[1], Cevdet Aydin[2], Nagihan Bestepe[2], Reyhan Ersoy[2] & Bekir Cakir[2]
[1]Department of Endocrinology and Metabolism, Ataturk Education and Research Hospital, Ankara, Turkey; [2]Department of Endocrinology and Metabolism, School of Medicine, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey.

Introduction
47,XYY syndrome is characterized by an extra copy of the Y chromosome in each cells of a male. It occurs in about 1/1000 of newborn boys and most males with this syndrome have normal sexual development and fertility. They tend to have tall stature and mild motor and language developmental problems. Testosterone levels are normal. Increased rate of criminal activity in XYY males was related to a lack of judgement and lower socioeconomic status due to a lower mean IQ score.
Case report
A 21 year-old-man applied to our clinic with complaints of small testis and penis and, lack of beard and ejaculation. He had normal libido and erection. There was no family history of infertility. He had not commited any crime. In physical examination, he had eunuchoid habitus, his height was 178 cm, weight was 66.6 kg, and BMI was 21 kg/m^2. His testes were palpable in the scrotum. Axillary and pubic hair development were consistent with Tanner stage 4. Penis length was 6.5 cm. His neurocognitive development were normal. Hormonal tests revealed hypogonadotropic hypogonadism. Other hypophyseal hormones were normal. Bone age was 14 years and epiphyseal plates were open. In testicular ultrasonography, volumes were 8 ml on the right and 7.5 ml on the left. Hypophyseal MRI showed partially empty sella. In chromosomal analysis, 47,XYY karyotype was detected. After administration of human chorionic gonadotropin treatment, androgen levels increased and ejaculation started although in small amounts (<0.5 ml).
Conclusion
Men with 47,XYY syndrome have a diverse spectrum of clinical presentation and because of the heterogeneous phenotype and lack of specific symptoms, its diagnosis may be difficult. As presented in our case, hypogonadotropic hypogonadism might be a presenting feature in patients with 47,XYY genotype.

DOI: 10.1530/endoabs.37.EP174

EP175

Endocrine disorders in women with Turner syndrome

Agnieszka Zwolak[1,2], Anna Dabrowska[1] & Jerzy Tarach[1]
[1]Chair and Department of Endocrinology, Medical University of Lublin, Poland, Lublin, Poland; [2]Chair of Internal Medicine and Department of Internal Medicine in Nursing, Medical University of Lublin, Poland, Lublin, Poland.

Introduction
Turner syndrome (TS) is the most common chromosomal abnormality in women. It occurs in 1/2500 to 1/3000 live-born females and results from a total or partial absence of the X chromosome. The clinical manifestations are diverse and TS is accompanied by multiple medical problems.
Methods
We analysed retrospectively six cases of women with TS aged 20–66 years, treated at Endocrinology Department between 2003 and 2014, to describe endocrine disorders in such patients. In the studied subjects, the diagnosis of TS was made in childhood (one patient), in adolescence (three cases) or in adulthood (two women), based on clinical symptoms and genetic tests.
Results
Short stature was diagnosed in all patients, three of them received recombinant human GH. The average height was 152.5 ± 6.53 cm. None of women were obese (BMI: 24.12 ± 2.88 kg/m^2). We stated primary amenorrhea in five patients, in one case premature ovarian insufficiency was observed. Clitoromegaly was found in one patient, in another case leukoplakia vulvae was diagnosed. Sex hormone replacement therapy was used by four women, two the oldest non-treated patients suffered from osteoporosis. Hypothyroidism due to Hashimoto's thyroiditis developed in five cases and they used levothyroxine. Diabetes mellitus (type 1 and type 2) appeared in two women. Patient with type 1 diabetes had many diabetic complications such as: coronary heart disease, cerebrovascular disease, peripheral vascular disease, sensory neuropathy, diabetic amyotrophy, glaucoma, cataract. One women was operated because of non-functioning pituitary adenoma. Moreover other non-endocrine diseases were observed, including: coeliac disease (two cases), hypertension (three patients), mitral incompetence and tricuspid regurgitation (one woman), impaired hearing (two subjects), ectopic or horseshoe kidney (two cases). The intellectual performance was within the normal range in four women, two patients were mentally retarded.
Conclusion
Most of subjects with TS have hormonal disorders. Therefore, endocrine care is needed to optimise patients' treatment.

DOI: 10.1530/endoabs.37.EP175

EP176

***In vitro* effects of aspartic acid, coenzyme Q10 and zinc on sperm function**

Filippo Giacone, Rosita Condorelli, Sandro La Vignera & Aldo Eugenio Calogero
Department of Clinical and Experimental Medicine, Catania, Sicily, Italy.

Introduction
D-aspartic acid (D-AA) is involved in the regulation of spermatogenesis by influencing hormonal biosynthesis and secretion, resulting in an increased sperm concentration and progressive motility. Coenzyme Q10 (CoQ10) correlates positively with sperm concentration and motility at high concentrations, and it plays an antioxidant role, improving sperm motility and fertilization rate in ICSI cycles. Finally, low concentrations of zinc (Zn) have been found in azoospermic patients, while higher concentrations improve sperm motility, concentration and viability. On these premises, the aim of this study was to evaluate the *in vitro* effects of these three compounds on spermatozoa.
Methods
We enrolled ten patients with oligo-astheno-teratozoospermia (OAT) and five normozoospermic subjects (age range: 20–45 years), without infection/inflammation of the male accessory glands, varicocele or other andrological diseases. Spermatozoa were incubated for 3 h with BWW (group A), BWW + ethanol + PBS (group A1) (control groups) or D-AA (500 mg/ml), CoQ10 (40 mg/ml) and Zn (10 g/ml) (group B). After incubation, the following parameters were assessed: sperm progressive motility, non conventional sperm parameters (mitochondrial membrane potential, degree of viability and/or apoptosis, sperm DNA fragmentation, lipid peroxidation). Subsequently, sperm selection was performed by swim-up technique in all groups.
Results
In OAT, progressive motility and the number of motile spermatozoa recovered by swim-up increased in group B compared to groups A and A1 ($P<0.05$). This was associated with an improvement of lipid peroxidation in group B vs A or A1

($P<0.05$). The other sperm parameters did not change. No significant change was observed in normozoospermic subjects.
Conclusions
These results showed that D-AA + CoQ10 + Zn act with antioxidant mechanism, ensuring a higher rate of motile spermatozoa recovered after swim-up, probably related to the improvement of progressive motility. These results suggest the use of this combination in both *in vivo*- and *in vitro*-assisted reproductive techniques.

DOI: 10.1530/endoabs.37.EP176

EP177

The effect of androgen replacement therapy on platelet aggregation in male patients with isolated hypogonadotropic hypogonadism

Ayten Oguz[1], Dilek Tuzun[1], Murat Sahin[1], Numan Guvenc[2], Elif Inanc[3], Irem Gokalp[3] & Kamile Gul[1]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey; [2]Department of Family Medicine, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey; [3]Department of Internal Medicine, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey.

Aim
To evaluate the effect of androgen replacement therapy on lipid profile and platelet aggregation in in male patients with isolated hypogonadotropic hypogonadism (IHH).
Material and methods
36 male patient, mean age 32.2 (18–54)with IHH, admitted to the outpatient clinic of Endocrinology and Metabolism were included to the study. Patients in the study were divided into two groups as Testosterone ($n=18$) and human chorionic gonadotropin (HCG) therapy ($n=18$) groups. Total testosterone, fasting plasma glucose (FPG), alanine aminotransferase (ALT), lipid profile, mean platelet volume (MPV), platelet distribution width (PDW) and platelet count were evaluated before and after 6 months of the treatment in all patients.
Results
There was no statistically significant difference according to FPG, triglyceride levels, MPV and platelet counts when all patients ($n=36$) were evaluated due to pre-treatment and post-treatment ($P>0.05$). However, ALT and LDL levels were detected statistically significantly lower after treatment ($P>0.05$), HDL, PDW and testosterone levels were significantly higher after treatment ($P<0.05$). There was no significant difference due to testosterone, FPG, ALT, lipid profile, MPV, PDW and platelet levels compared according to treatment (HCG ($n=18$), and testosterone replacement ($n=18$)) ($P>0.05$). While there was negative correlation with testosterone and ALT levels ($r=-0.25$, $P=0.03$), positive correlation was detected between testosterone and PDW ($r=0.31$, $P=0.007$).
Conclusion
Platelets are involved in homeostatic process and have an important role in atherosclerosis and arterial thrombosis. MPV and PDW are two markers of platelet activation, and have recently been recognised as risk predictors of cardiovascular diseases. Our study revealed that androgen replacement therapy may have beneficial effects on lipid profile and ALT and negative effects on platelet aggregation. Therefore, we think that this situation should be taken into consideration when androgen replacement therapy is planned.

DOI: 10.1530/endoabs.37.EP177

EP178

Visceral adiposity index – new anthropometric marker in women with polycystic ovary syndrome: preliminary reports

Anna Bronczyk-Puzon[1], Pawel Jagielski[2], Karolina Kulik-Kupka[1], Justyna Nowak[1], Aneta Koszowska[1] & Barbara Zubelewicz-Szkodzinska[1]
[1]Department of Nutrition-Associated Disease Prevention, Faculty of Public Health, Medical University of Silesia, Katowice, Poland; [2]Faculcy of Clinical Biochemistry, Institute of Genetic Diagnostics and Nutrigenomics, Collegium Medicum of Jagiellonian University, Krakow, Poland.

Introduction
Early detection of carbohydrate and fat metabolism disorders in women with polycystic ovary syndrome allows the early prevention of cardiovascular diseases and type II diabetes.
Aim
The purpose of this study was to assess the selected metabolic indicators and anthropometric measurements in two groups of women: metabolically healthy polycystic ovary syndrome (MH-PCOS) and metabolically unhealthy PCOS (MU-PCOS).
Materials and methods
Cross sectional study was conducted in a group of 44 women hospitalized in the endocrinology department who met the Rotterdam criteria of PCOS syndrome. Tested women were divided into a MH-PCOS (VAI <1.675) group and a MU-PCOS (VAI >1.675) group. Body composition was analyzed via bioelectrical impedance analysis (BIO). During the statistical analysis it was assumed that $\alpha=0.05$.
Results
Examined women, was at age 18–38 years (26.52 ± 5.73). The average age of the MH-PCOS group was 26 (22.5–31) and 25.27 ± 5.57 ($P>0.05$) in the MU-PCOS group. The study showed statistically significant differences between the MU-PCOS group and the MH-PCOS group in term of values: body mass (87.04 ± 19.12 vs 61.3 (54.9–70.25); BMI indicator (32.61 ± 6.44 vs 22.85 (20.7–25.25); $P=0.001$), waist circumference (100.5 ± 16.03 vs 79.52 ± 11.9; $P<0.01$), serum triglyceride concentration (1.6 (1.37–2.03) vs 0.81 ± 0.26; $p=0.001$), HOMA IR (2.72 ± 1.21 vs 1.66 (1–2.5); $P=0.0387$). Statistically, the average value of HDL cholesterol was significantly lower in the MU-PCOS group than in the MH-PCOS group (1.16 ± 0.09 vs 1.83 ± 0.39) ($P<0.01$). In the study, a statistically significant positive correlation was noticed between the Visceral Adiposity Index (VAI) value and the body mass ($r=0.69$), the insulin level ($r=0.46$) and the HOMA IR indicator ($r=0.33$) ($P<0.05$ for all).
Conclusion
Visceral Adiposity Index may be an easy and effective tool to assess metabolically unhealthy women with PCOS in the daily diet and medical practice.

DOI: 10.1530/endoabs.37.EP178

EP179

Evaluation of most common symptoms and findings in Turkish adolescent girls with polycystic ovary syndrome

Mina Gulfem Kaya[1], Cevdet Aydin[2], Sefika Burcak Polat[1], Duriye Deniz Demirseren[3], Reyhan Ersoy[2] & Bekir Cakir[2]
[1]Department of Endocrinology and Metabolism, Atatürk Education and Research Hospital, Ankara, Turkey; [2]Department of Endocrinology and Metabolism, Yildirim Beyazit University Faculty of Medicine, Ankara, Turkey; [3]Department of Dermatology, Atatürk Education and Research Hospital, Ankara, Turkey.

Objective
Polycystic ovary syndrome (PCOS) is a complex endocrinopathy affecting 5–10% of women in reproductive period. Our goal is to determine which symptoms and findings are the most common in Turkish adolescents with PCOS.
Material and method
Ninety three adolescents (15–19 years old) who admitted to our outpatient clinic with at least one of the complaints (acne, obesity, menstrual irregularities and hirsutism) were enrolled in the study. All patients were evaluated due to both Rotterdam and NIH criteria.
Results
Due to Rotterdam and NIH criteria 40 (43.01%) and 32 (34.40%) of patients were diagnosed as PCOS respectively. Due to Rotterdam menstrual irregularities were 90%, hirsutism was 45%, obesity was 25% and acne was 32.5% in patients diagnosed as PCOS. Due to NIH these ratios were 96.9, 50, 25 and 31.3% respectively. Patients were divided into 12 subgroups due to combinations of complaints. Due to Rotterdam, PCOS diagnosis were 100% for menstrual irregularities and hirsutism together, 75% for menstrual irregularities and acne together, 66.7% for menstrual irregularities and obesity together, 66.7% for only hirsutism, 50% for hirsutism and acne together, 40% for only menstrual irregularities, 3.7% for only acne and 0% for only obesity. Due to NIH, PCOS diagnosis were 100% for menstrual irregularities and hirsutism together, 66.7% for menstrual irregularities and acne together, 44.4% for menstrual irregularities and obesity together, 33.3% for only hirsutism, 26.7% for only menstrual irregularities, 0% for only acne or only obesity. Eight patients were diagnosed as PCOS only due to Rotterdam.
Conclusion
The most common complaints in Turkish adolescents with PCOS were menstrual irregularities, hirsutism, acne and obesity in our study. According to guidelines PCOS in adolescents is based on clinical and/or laboratory hyperandrogenism together with persistent oligomenorrhoea. Polycystic ovarian morphology can be a part of reproductive changes in adolescents.

DOI: 10.1530/endoabs.37.EP179

EP180

Post load insulin vs fasting levels in prediction of type 2 diabetes in women with PCOS

Mirjana Sumarac-Dumanovic[1,2], Dragan Micic[1,2], Danica Stamenkovic-Pejkovic[1,2], Ana Gligic[2], Danka Jeremic[2], Jelena Milin-Lazovic[1] & Goran Cvijovic[1,2]
[1]School of Medicine, University of Belgrade, Belgrade, Serbia; [2]Clinic for Endocrinology, Diabetes and Diseases of Metabolism, Belgrade, Serbia.

Introduction
Women with polycystic ovary syndrome (PCOS) are at increased risk of developing insulin resistance (IR) and T2DM. In this study, we attempted to detect IR parameters that could be the best predictor T2DM in PCOS comparing to controls.
Description of methods/design
In 130 women with PCOS (BMI = 29.7 ± 0.66 kg/m^2; age: 25.6 ± 0.59 years) and 41 controls (age and BMI matched) (BMI = 28.5 ± 1.35 kg/m^2; age: 26.5 ± 0.89 years) OGTT and IVGTT (minimal model analyses) were performed. All women has normal fasting glucose, but 16 PCOS women had post load glucose level (120 min) over 7.8 mmol/l.
Results
After excluding PCOS women with IGT, there was no difference between fasting glucose, but glucose at 2 h (OGTT) were still higher in PCOS ($P < 0.05$). Fasting insulin was significantly higher in PCOS (PCOS vs control) (17.02 ± 1.07 vs 12.54 ± 1.72) as well as insulin at 120 min of OGTT (86.85 ± 7.18 vs 56.31 ± 10.57). There was no statistically significant difference between areas under insulin curve between two groups (10417.12 ± 733.14 vs 8098.36 ± 1098.2). Minimal model confirmed no difference in IV glucose tolerance (kg) between PCOS and controls and in acute insulin response (AIR). Si parameter of insulin sensitivity was significantly lower in PCOS (2.46 ± 0.18 vs 3.59 ± 0.39). Disposition index (DI) were significantly higher in controls (166.57 ± 13.9 vs 220.89 ± 33.47). Additional analyses of two PCOS subgroups with normal (NGT) and impaired glucose tolerance (IGT) showed: significant lower Si in IGT subgroup, not different AIR, lower DI. The best correlation with Si (from minimal model) showed OGIS (0.490, $P < 0.01$) (glucose 0.90 i 120 min and insulin at 0 and 90 min), weaker correlation showed HOMA index (0.271; $P < 0.01$) and fasting insulin (−0.247, $P < 0.01$).
Conclusion
These insulin sensitivity indexes could be potentially used to identify subgroups of insulin resistant PCOS women with increased risk of T2DM. Our result suggests that indexes included basal and post load glucose and insulin constitute a more sensitive tool for screening metabolic abnormalities in PCOS.

DOI: 10.1530/endoabs.37.EP180

EP181

Ameliorated effects of allium sativum against bisphenol A-induced reproductive toxicity in male rats

Mokhtar Ibrahim Yousef[1], Al-Sayeda A Newairy[2], Afrah F Salama[3] & Shaimaa E M Saber[3]
[1]Department of Environmental Studies, Institute of Graduate Studies and Research, Alexandria University, 163 Horreya Avenue, Chatby 21526, PO Box 832, Alexandria, Egypt; [2]Department of Biochemistry, Faculty of Science, Alexandria University, Alexandria, Egypt; [3]Chemistry Department, Biochemistry Section, Faculty of Science, Tanta University, Tanta, Egypt.

There is growing evidence that bisphenol A (BPA) may adversely affect humans. BPA is an endocrine disruptor that has been shown to be harmful in laboratory animal studies. A comprehensive literature search found 91 studies linking BPA to human health; 53 published within the last year. This body of literature is showing associations between BPA exposure and adverse perinatal, childhood, and adult health outcomes, including reproductive and developmental effects, metabolic disease, and other health effects. These studies encompass both prenatal and postnatal exposures, and include several study designs and population types. But until recently, there were relatively few studies examining the effect of BPA on sperm quality and the protective effects of antioxidants against its reproductive toxicity. Thus, present examination tries to assess powerful antioxidant garlic against BPA. Rats were assigned to one of four groups: 0 mg BPA and 0 g garlic/kg BW (control); 2 g garlic/kg BW; 40 mg BPA/kg BW; BPA plus garlic. Rats were orally administered their respective doses daily for 70 days. BPA caused deterioration in semen characteristics and histological changes in testes. Body weight, plasma acid phosphatase, LH and FSH were increased, while total proteins, testosterone and sex organ weights (testes, epididymis, prostates and seminal vesicles) were significantly decreased. BPA increased thiobarbituric acid-reactive substances (TBARS) and decreased the activities of the antioxidant enzymes. Testicular 17-ketosteroid reductase, acid phosphatase and protein content were decreased, while 17β-hydroxysteroid dehydrogenase was increased. Garlic alone reduced TBARS, induced the activities of the antioxidant enzymes and improved semen characteristics. Administration of garlic with BPA intoxicated rats reduced the testicular toxic condition, morphological and biochemical changes were brought back to normal. In termination, antioxidant potential of garlic, ameliorates the changes that are induced by BPA.

DOI: 10.1530/endoabs.37.EP181

EP182

Is serum estradiol really increased in patients with Klinefeler syndrome? Results from a meta-analysis study

Daniele Santi, Sara Scaltriti & Vincenzo Rochira
Unit of Endocrinology, Department of Biomedical, Metabolic, and Neural Sciences, University of Modena and Reggio Emilia, Azienda USL of Modena, Modena, Italy.

Background and aim
KS has been classically described as characterized by hyperestrogenism and elevated serum E_2 together with increased gonadotropins and low-to-normal serum testosterone (T). In literature, data on increased serum E_2 are not solid. The aim of this study is to meta-analyse data from studies evaluating serum E_2 in both KS and healthy subjects (HS) in order to verify if E_2 is increased in KS.
Methods
An extensive MEDLINE was performed using 'PubMed' with the following key words: 'KS' and 'E_2' or 'T' or 'sex steroids' from 1946 to January 2015 (current contents-ISI was used for searching oldest studies). All studies (case–control, case–series, case–reports) reporting E_2 measurement were considered. Controlled–studies were used for meta-analysis, the others only for reviews. Only serum E_2 at baseline (no ongoing treatments) was included. Meta-analysis was conducted according to the PRISMA statement using RevMan.
Results
Out of 956 articles, 26 case–control studies, 15 case–series and 21 case–reports had data on serum E_2. A total of 878 KS and 1000 HS were included in the meta-analysis. Serum E_2 was significantly higher in HS than in KS, with a mean difference of 7.93 pg/ml (CI: 2.24, 13.61; $P = 0.006$), with a $\chi^2 = 688.32$ (I-square = 97%). Serum T was significantly lower in KS than in HS, with a mean difference of −2.79 ng/ml (CI: −3,46, −2,11; $P < 0.001$), with a $\chi^2 = 198,29$ (I-square = 89%). Data from case–series and case–reports confirmed that E_2 is not above the normal range in KS.
Conclusions
Serum E_2 is not increased in KS and is significantly lower than in HS in this meta-analysis. The limits of this study are the heterogeneity of methods for steroids measurement and the lack of studies having the comparison of serum E_2 between KS and HS as primary endpoint. The traditional belief that KS is associated to elevated E_2 should be reconsidered together with some pathophysiological and clinical issues.

DOI: 10.1530/endoabs.37.EP182

EP183

Relationship between diabetes mellitus type 1 and male reproductive function

Sandro La Vignera
Department of Clinical and Experimental Medicine, Catania, Italy.

Diabetes mellitus type 1 (DM1), an autoimmune disease, affects an increasing number of young men in reproductive age. It has been estimated that its

prevalence increases at a rate of ~3% per annum. Diabetes may affect male reproductive function by acting on the hypothalamic-pituitary-testicular axis, causing sexual dysfunction and disrupting male accessory gland function. According a recent study shows that men with DM1 have a smaller number of live births than controls. Despite such evidence, little is known about sperm parameters (mainly limited to conventional sperm parameters) and other aspects of the male reproductive function in these patients. Therefore, this study was undertaken to evaluate both conventional and non-conventional sperm parameters, serum gonadal hormones and didymo-epididymal ultrasound features in patients with DM1. To accomplish this, 30 patients with DM1 (aged 18–35 years) and 20 age-matched fertile healthy men were enrolled in this prospective study. Patients with diabetic neuropathy, other endocrine disorders or conditions known to alter sperm parameters were excluded from the study. Conventional sperm parameters were evaluated according to the WHO 2010 criteria. As far non-conventional sperm parameters, mitochondrial function (mitochondrial membrane potential, MMP), apoptosis and chromatin/DNA integrity were evaluated by flow cytometry following specific staining. Serum total testosterone, 17β-oestradiol, LH, FSH and prolactin were measured in all patients and controls. Finally, testicular and epididymal morphometry was evaluated by ultrasound scan before and after ejaculation. Patients with DM1 had a significantly lower percentage of spermatozoa with progressive motility than controls. This abnormality was significantly lower in DM1 patients with long (>10 years) than short (<5 years) disease duration. In addition, the percentage of spermatozoa with high MMP was significantly lower in DM1 patients than in controls. This non-conventional parameter was significantly worse in patients with long or intermediate (5–10 years) vs short DM1 duration. Disease duration correlated inversely with the percentage of spermatozoa with high MMP. Patients with DM1 had a significantly higher cephalic and caudal epididymal diameters after ejaculation compared to controls, suggesting a lack of the physiological epididymal post-ejaculatory shrinkage. This aspect of the epididymal physiology was significantly more compromised in patients with long vs short disease duration. All the other parameters did not show any statistically significant difference. Finally, HbA1c did not correlate with any of the parameters evaluated. In conclusion, patients with DM1 had lower sperm progressive motility, impaired mitochondrial function (which precedes the onset of motility disturbance) and epididymal post-ejaculatory dysfunction which cannot be ascribed to endocrinopathy and/or neuropathy. These findings may explain why patients with DM1 experience fertility disturbance.

DOI: 10.1530/endoabs.37.EP183

EP184

Serum dihydrotestosterone equivalent levels in women: a new index of hyperandrogenemia

Yeon-Ah Sung[1], Do Kyeong Song[1], Sei Hyun Baik[2] & Dong Sun Kim[3]
[1]Ewha Womans University, Seoul, Republic of Korea; [2]Korea University, Seoul, Republic of Korea; [3]Hanyang University, Seoul, Republic of Korea.

The measurement of androgens is critical for the diagnosis of polycystic ovary syndrome (PCOS) but it has been difficult based on poor specificity and sensitivity of assays in the female range. The direct total androgen activity can be measured with dihydrotestosterone equivalent concentration (DEQ) using chemically activated luciferase gene expression (CALUX) bioassays. The aim of the study is to determine whether DEQ levels can be the index for hyperandrogenemia to be required for diagnosis of PCOS. The study involved 100 women with PCOS and 100 healthy women with regular menstrual cycles. The initial evaluation including case history, anthropometrical data, excess facial and body hair and two-dimensional vaginal ultrasound was assessed. All hormonal investigations (T, total testosterone; A, androstenedione; fTc, calculated free testosterone from T and SHBG; DEQ levels by CALUX bioassay) were performed. A correlation of T ($r=0.3912$, $P<0.001$), A ($r=0.41$, $P<0.001$) and fTc ($r=0.45$, $P<0.001$) with DEQ levels. DEQ levels were significantly higher in women with PCOS compared to controls ($P<0.05$). Increased levels (95percentile of serum levels in control women) of T, fTc, A and DEQ were noted in 73, 71, 69 and 82% in women with PCOS, respectively. A total of 98% of the subjects with the highest quartile of DEQ levels had PCOS. The optimal DEQ cutoff value for predicting PCOS was 151.9 pg/l (96.0% sensitivity, 87.0% specificity) and the area under the ROC curve was 0.97 (95% confidence interval, 0.94–0.99). The DEQ levels were correlated with ovarian volume ($r=0.51$, $P<0.001$) and ovarian follicle number ($r=0.58$, $P<0.001$), total cholesterol ($r=0.21$, $P=0.004$), LDL cholesterol ($r=0.16$, $P=0.022$), fasting plasma insulin ($r=0.31$, $P=0.002$), post-load 2-h plasma insulin ($r=0.21$, $P=0.034$). DEQ levels may be a good indicator of hyperandrogenemia in women. We also confirm that measurement of DEQ levels in serum can be useful in making a diagnosis of PCOS.

DOI: 10.1530/endoabs.37.EP184

EP185

Eating habits of women without hormonal contraception depends on menstrual cycle - preliminary report

Anna Spalik-Bytomska[1], Justyna Nowak[2], Aneta Koszowska[2], Anna Bronczyk-Puzon[2], Karolina Kulik-Kupka[2], Agata Kulpok[3] & Barbara Zubelewicz-Szkodzinska[2,3]
[1]Faculty of Public Health, Medical University of Silesia, Katowice, Poland; [2]Department of Nutrition-Associated Disease Prevention, Faculty of Public Health, Medical University of Silesia, Katowice, Poland; [3]Department of Endocrinology, Country Hospital Piekary Slaskie, Piekary Slaskie, Poland.

Introduction
Hormonal changes during menstrual cycle among women without hormonal contraception could probably influence the food intake. Sex hormones modulate body energy expenditure by affecting hypothalamus neurohormones.
Aim
The aim of the study was to assess the way of nutrition among menstruating women without hormonal contraception, depend of menstrual cycle.
Materials and methods
77 menstruating women in age 19–26 entered the study. The way of nutrition (caloric intake, protein, fat, carbohydrates content) was assessed in each phases of menstrual cycle (menstrual phase, ovulatory phase, luteal phase). The 24 h feeding interview was used. The collected data were statistically analysed, $\alpha=0.05$.
Results
The mean of age was 22.79 ± 1.94 years. The mean of caloric intake in menstrual phase was 1825.65 ± 471.97 kcal, ovulatory phase 1842.28 ± 391.74 kcal, luteal phase 2225.82 ± 551.30 kcal. The mean fat intake in menstrual phase was 66.44 ± 27.06 g, ovulatory phase 70.32 ± 25.40 g; luteal phase 88.44 ± 40.38 g. The mean carbohydrates intake in in menstrual phase 247.89 ± 72.62 g, ovulatory phase 244.73 ± 57.54 g, luteal phase 290.18 ± 68.16 g. The statistical significance difference was observed between energy intake in particular cycle phases ($P<0.0001$). Moreover the statistical significance differences were also observed between fat intake ($P<0.0001$) and carbohydrate intake ($P<0.0001$).
Conclusion
The way of nutrition among women without hormonal contraception depend on phases of menstrual cycle. In the luteal phase intake of carbohydrates including sugars was the highest. This observation could be helpful for maintaining a proper weight by better controlling of food intake.

DOI: 10.1530/endoabs.37.EP185

EP186

Relationship between polycystic ovary syndrome and platelet distribution width

Özgür Yilmaz[1], Muzaffer Temur[1], Mehmet Calan[2], Elif Pelin Özün Özbay[3], Murat Karakulak[4] & Tuncay Kume[5]
[1]Department of Obstetrics and Gynecology, Manisa Merkezefendi Hospital, Manisa, Turkey; [2]Department of Endocrinology, Izmir Bozyaka Research Hospital, Izmir, Turkey; [3]Department of Obstetrics and Gynecology, Aydin Obstetrics and Pediatrics Hospital, Aydin, Turkey; [4]Department of Obstetrics and Gynecology, Silivri State Hospital, Istanbul, Turkey; [5]Department of Medical Biochemistry, Dokuz Eylul University Medical School, Izmir, Turkey.

Purpose
Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive period, and it has been considered as a risk factor in cardiovascular disease due to increased prevalence of hypertension, dyslipidaemia, obesity, and insulin resistance. Platelets have a pivotal role in the

development of atherothrombosis. Platelet distribution width (PDW) is a marker of platelet size that reflects the heterogeneity of the platelets. This arithmetical index routinely analyses as part of a whole blood count without additional costs. In this study we purposed whether PCOS associated with PDW.
Materials and methods
Cross-sectional study of 119 healthy women with regular menses and 133 women with PCOS age- and BMI-matched. Waist and hip circumferences, body fat percentage, CBC, plasma fasting glucose, insulin, high sensitive C-reactive protein (hs-CRP), lipids, and total testosterone levels were measured. In multivariate linear regression model, PCOS was defined as a dependent variable and PDW and other platelet indices such as mean platelet volume and platelet large cell ratio were determined as independent variables.
Results
PDW levels were significantly higher in the PCOS group compared with the control group ($13.648 \pm 0.424\%$ vs $13.447 \pm 0.489\%$; $P=0.003$) PDW levels were not correlated with hs-CRP, HOMA-IR, and BMI ($P>0.005$). According to linear regression model, only PDW was associated with PCOS ($R^2=0.05$, $\beta=0.177$, $P=0.022$).
Conclusions
PDW levels were significantly higher in women with PCOS; however this index was correlated with neither HOMA-IR nor hs-CRP which is recognized as a cardiovascular risk factor in PCOS. PDW was associated with PCOS; however higher PDW levels cannot be considered as a cardiovascular risk factor in PCOS.

DOI: 10.1530/endoabs.37.EP186

EP187

Clinical significance of ADAMTS1, ADAMTS5, ADAMTS9 aggrecanases and IL17, IL23, IL33 cytokines in polycystic ovary syndrome

Melia Karakose[1], Kadir Demircan[2], Esra Tutal[1], Taner Demirci[1], Muyesser Sayki Arslan[1], Mustafa Sahin[3], Huseyin Tugrul Celik[4], Fatmanur Kazanci[4], Erman Cakal[1] & Tuncay Delibasi[1,5]
[1]Department of Endocrinology and Metabolism, Diskapi Teaching and Research Hospital, Ankara, Turkey; [2]Department of Medical Biology, Turgut Ozal University School of Medicine, Ankara, Turkey; [3]Department of Endocrinology and Metabolism, Ankara University School of Medicine, Ankara, Turkey; [4]Department of Biochemistry, Turgut Ozal University School of Medicine, Ankara, Turkey; [5]Department of Internal Medicine, Hacettepe University School of Medicine, Kastamonu, Turkey.

Introduction
Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among women of reproductive age. A disintegrin and metalloproteinase with thrombospondin-like motifs (ADAMTS) are involved in inflammation and fertility. The aim of this investigation was to evaluate to serum levels of ADAMTS1, ADAMTS5, ADAMTS9, IL17, IL23, IL33 and to find out the relationship between these inflammatory cytokines and ADAMTSs in PCOS patients.
Methods
Eighty patients with PCOS and 78 healthy female volunteers were recruited in the present study. Serum ADAMTS and IL levels were determined by a human ELISA in all subjects.
Results
The ADAMTS1 level was significantly lower and IL17A, IL23 levels were significantly higher in the PCOS patients compared to the controls ($P<0.05$). We could not find significant difference between the groups in terms of ADAMTS5, ADAMTS9, and IL33 levels. ADAMTS1 and ADAMTS9 had negative correlations with age, BMI, and waist/hip ratio. IL17A had positive correlation with total cholesterol and LDL.
Conclusion
The understanding of the molecular organization and function of ADAMTS in patients diagnosed with PCOS, which has an unknown pathogenesis, gains an importance and emerging hot topic. Based on the results of the present study, ADAMTSs and ILs might have key roles in PCOS pathogenesis. Further efforts are needed to establish causality for ADAMTS–IL axis.
Disclosure
This study has received financial support from TUBITAK (grant number 114S039, 2014).

DOI: 10.1530/endoabs.37.EP187

EP188

Effects of thiouracil compounds on chemically induced rat mammary gland carcinogenesis

Dana Macejová[1], Slavomíra Ondková[1], Ján Líška[1,2] & Július Brtko[1]
[1]Institute of Experimental Endocrinology SAS, Bratislava, Slovakia; [2]Medical Faculty, Institute of Histology and Embryology, Comenius University, Bratislava, Slovakia.

Introduction
Thyroidal status can play important role in progression mammary gland tumour growth. We have already shown that hypothyroidism induced by application of 6-*n*-propylthiouracil (PTU) – inhibitor of type I iodothyronine 5′-deiodinase (5′-DI) – prolonged tumour latency and reduced number, volume and burden of 1-methyl-1-nitrosourea (MNU) induced rat mammary gland tumours in Sprague–Dawley female rats.[1]
Design
4-Hydroxy-2-mercapto-6-methylpyrimidine (MTU) is a derivative of PTU, thus the effects of PTU or MTU on tumour progression as well as expression of selected nuclear receptors in MNU-induced mammary gland tumours and rat livers were investigated in this experiment. Female Sprague–Dawley rats were given 50 mg/kg MNU i.p. on 62nd, 109th, and 150th day of age. From 56th day of age, the PTU group of MNU treated rats was receiving PTU (1 mg/kg) intragastrically 3× per week and MTU group of MNU animals 0.1% w/v of MTU in drinking water until the end of experiment.
Results
Administration of PTU to MNU treated animals markedly reduced number of tumours when compared to MNU group of animals. Furthermore, we did not find any tumour in the MTU group of animals. However we have detected significantly reduced body weight when compared to PTU, untreated MNU animals and healthy control animals. Administration of MTU resulted in reduced expression of RARα, RXRα and increased expression of RARγ in rat liver (vs MNU and C). Using EMSA method, we have found significantly reduced amount of nuclear receptor-hormone responsive elements (RARE, TRE, and VDRE) complex in tumours of PTU treated animals (vs MNU animals). Since MTU did not affect 5′-DI in the liver, the mechanism of MTU action needs further investigation.
Disclosure
This work was supported by the grant APVV-0160-11, the VEGA grant 2/0171/14, and the Centre of Excellence CEMAN grant.
Reference
1. Macejova *et al. Mol. Cell. Endocrinol.* 2005 **244** (1–2) 47–56.

DOI: 10.1530/endoabs.37.EP188

EP189

The role of tailored treatment on conception and pregnancy at patients with insulin resistance

Katalin Nas, Helga Breyer & László Tűű
Mens Mentis EC, Budapest, Hungary.

Patients with insulin resistance are often confronted with conception difficulties. Our database of 1178 conceivable female patients with metabolic disorder shows that more than 40% of them suffer from menstrual cycle disorders. More than 25% out of 480 pregnant women with hyperinsulinaemia had at least one assisted reproduction procedure in their lives. 42% of patients with insulin resistance experienced missed abortion, out of them 26% one time, 12% two times. Our aim was to provide a complex and tailored treatment to women with insulin mediated metabolic disorder who desired pregnancy. The tailored treatment consisted of diet, physical exercises based on BMI and body constitution, medical treatment (if needed) and coaching. Setting BMI goals between 20 and 24, the outstanding role of dietary treatment is remarkable: patients attending (not necessarily following!) dietary counselling became pregnant up to 90%, while patients not attending these consultations were successful up to 68%. Owing to this complex and tailored method more than 71% out of 224 women became pregnant. Pregnancy rates were different according to ages: 75% up to 35 years of age, getting less to 43% above 40 years of age. During pregnancy the complex tailored treatment continued. GDM occurred in 39%of the cases. Mothers with former PCOS developed GDM up to 36%. The average birth weight of the babies was 3321 g. The complex tailored treatment requires a close follow-up and interactive cooperation.

DOI: 10.1530/endoabs.37.EP189

EP190

Eating pattern does not depend on the menstrual cycle phase in a group of women taking hormonal contraceptives: preliminary reports

Anna Spalik-Bytomska[1], Justyna Nowak[2], Anna Bronczyk-Puzon[2], Aneta Koszowska[2], Karolina Kulik-Kupka[2], Anna Dittfeld[3] & Barbara Zubelewicz-Szkodzinska[2]
[1]Faculty of Public Health, Medical University of Silesia, Katowice, Poland; [2]Department of Nutrition-Associated Disease Prevention, Faculty of Public Health, Medical University of Silesia, Katowice, Poland; [3]Doctoral Study in the School of Medicine with the Division of Dentistry in Zabrze, Medical University of Silesia, Katowice, Poland.

Introduction
Sex hormones, such as estrogens or progesterone may have, both directly and indirectly, an influence on the appetite changes in. In addition, exogenous sex hormones are commonly used as one method of contraception.
Aim
The purpose of this study was to assess whether the eating style in a group of menstruating women, taking oral hormonal contraceptives, is different in the individual menstrual cycle phases.
Material and methods
28 menstruating women taking oral hormonal cantraceptives in age 19–25 were included to the study. The way of nutrition (caloric intake, protein, fat, and carbohydrates content) was assessed in each phases of menstrual cycle (menstrual phase, ovulatory phase, and luteal phase). The 24 h feeding interview was used. The collected data were statistically analyzed, $\alpha = 0{,}05$.
Results
The average age of surveyed women was 22.04 ± 1.86 years. The average daily energy consumption was in the: menstrual phase 1841.76 ± 562.67 kcal; ovulatory phase 1799.53 ± 501.36 kcal; and luteal phase 2052.58 ± 473.74 kcal. The average fat content was in the: menstrual phase 70.67 ± 31.46 g; ovulatory phase 65.88 ± 28.10 g; and luteal phase 79.89 ± 27.75 g. The average carbohydrates content was in the: menstrual phase 244.59 ± 79.88 g; ovulatory phase 247.96 ± 83.94 g; and luteal phase 273.73 ± 70.77 g. The average saccharose content was in the: menstrual phase 38.73 ± 21.66 g; ovulatory phase 42.41 ± 28.69 g; and luteal phase 64.28 ± 39.11 g. The saccharose content was statistically significantly different between the menstrual phase and the luteal phase ($P = 0.0077$) and the ovulatory phase and the luteal phase ($P = 0.0255$). The average daily energy consumption was not statistically significantly different in the individual cycle phases ($P = 0.0572$). Furthermore, there was not statistically significant differences between fat content ($P = 0.1178$) and carbohydrates content ($P = 0.1797$) between the individual menstrual cycle phases.
Conclusion
Oral hormonal contraceptives does not influence eating pattern of the examined women.

DOI: 10.1530/endoabs.37.EP190

EP191

The PCOS demographic in a dedicated University Hospital Clinic

Maeve Durkan[1,2] & Bernard Kennedy[1,2]
[1]Galway University Hospital, Galway, Ireland; [2]NUI Galway School of Medicine, Galway, Ireland.

This retrospective review of all adult women referred to a dedicated University Clinic for presumed polycystic ovarian syndrome (PCOS) aims to determine i) the true PCOS prevalence and ii) to evaluate baseline demographics by diagnostic criteria and their relationship to metabolic and cardiovascular risk parameters. All charts were reviewed. The diagnosis of PCOS rests on excluding another endocrinopathy, and fulfilling any two of the three criterias as per the Rotterdam statement, i.e. oligomenorrhoea, hyperandrogenism, and/or polycystic ovaries. We reviewed coexistent hypertension, dyslipidaemia, dysglycaemia, metabolic syndrome (MetS), and NAFLD in the proven PCOS cohort. The cohort was also divided into three groups based on their inclusion criteria: group 1 (oligomenorrhoea and hyperandrogenism), group 2 (oligomenorrhea and polycystic ovaries), and group 3 (hyperandrogenism and polycystic ovaries) and these factors assessed per category. 250 women were referred with a presumed diagnosis of PCOS. 134 (54%) had confirmed PCOS. The other 116 (46%) included ectopic Cushing's, prolactinoma, nonclassical CAH, PIH, POF, hypothalamic, and obesity driven oligomenorrhoea. The PCOS cohort had a mean systolic BP 124.78 (s.d. 15.8) and a mean diastolic BP 75.46 (s.d. 9.4). Mean age was 27.74 years (s.d. 6.7 years). Mean BMI was 31 (s.d. 8.34). 30.4% of the PCOS group were normal weight or underweight (BMI <24.9). 71.6% had a BMI >24.9 (21.6% overweight and 48% obese). Metabolic datasets were incomplete but 2.5% had pre-diagnosed DM2 and one patient was diagnosed at presentation. 9/54 patients evaluated had ↑ ALT/GGT. 120 patients met group 1 criteria, six met group 2 criteria, and four met group 3 criteria and 14 patients only met all three. 124/134 PCOS women had hyperandrogenism either biochemically alone (8), phenotypically alone (4) but most (113) having both. Hypertension was more prevalent in group 1 (20/120) vs group 2 (0/6) vs group 3 (0/4). The BMI range was higher in group 1 ($31.42 + 8.28$) and group 3 ($33.89 + 14.77$) vs group 2 ($25.52 + 5.59$) raising a question of a relationship to hyperandrogenism. Equally group 1 were more likely to have ↑ Tg levels (18/120 vs 1/6 vs 0/4), ↓ HDL (30/120 vs 1/6 vs 1/6) and MetS (10/120 vs 1/6 vs 0/6). 38 women having a BMI <25 had no hypertension or MetS. Of 60 women with a BMI >35, 13 had hypertension and 11 had MetS. This is the first review of an Irish cohort. It is striking that 30% of proven PCOS patients have a normal BMI undermining the assumption of obesity as a prerequisite phenotype. 90% were diagnosed with oligomenorrhoea and hyperandrogenism alone. In keeping with the international literature, this cohort has greatest metabolic risk mandating focused risk assessment and intervention. Our data is weakened by sporadic metabolic testing but nonetheless supports new guidelines recommending this. Finally, our results reiterate the principle of PCOS as a diagnosis of exclusion with almost 50% having a different underlying diagnosis.

Disclosure
Student research grant of 2000 euros from the Irish Endocrine Society.

DOI: 10.1530/endoabs.37.EP191

EP192

Hypercoagulable overall haemostatic potential is not intrinsically associated with PCOS but worsens with increasing BMI

Matej Rakusa[1], Mojca Jensterle[2], Andrej Janez[2] & Mojca Bozic Mijovski[3]
[1]Division of Internal Medicine, Department of Endocrinology and Diabetology, University Medical Centre Maribor, Maribor, Slovenia; [2]Division of Internal Medicine, Department of Endocrinology, Diabetes and Metabolic Diseases, University Medical Centre Ljubljana, Ljubljana, Slovenia; [3]Laboratory for Haemostasis and Atherothrombosis, University Medical Centre Ljubljana, Ljubljana, Slovenia.

Introduction
Growing evidences imply a role of coagulation system in the development of thromboembolic events and progression of atherosclerosis in PCOS. The aim of the study was to identify potential relationship of overall haemostatic potential (OHP) with a syndrome *per se*, BMI and androgens. OHP has not yet been assessed in PCOS.
Methods
In 89 women with PCOS aged 30.9 ± 8.1 years (50 obese, 13 overweight, and 27 normal weight) and 21 healthy age matched controls (11 obese and ten normal weight) OHP with overall coagulation potential (OCP) and overall fibrinolytic potential (OFP) was determined spectrophotometrically by repeated fibrin formation and degradation registration in two parallel plasma samples. OFP was calculated as $((OCP - OHP)/OCP) \times 100$ (%).
Results
OHP increased with BMI in PCOS (15.5 ± 3.8 in obese, 12.5 ± 5.1 in overweight, and 9.6 ± 2.3 Abs-sum in normal weight) and in controls (17.3 ± 4.6 in obese and 9.1 ± 1.0 in normal weight). There was significant difference between obese and normal weight PCOS ($P < 0.001$) and between obese and normal weight controls ($P < 0.001$). OCP also increased with BMI in PCOS (28.5 ± 5.2 in obese vs 25.7 ± 5.2 in overweight vs 22.6 ± 3.9 Abs-sum in normal weight; $P < 0.001$ for obese vs normal weight) and in controls (29.0 ± 7.1 in obese vs 22.3 ± 3.4 Abs-sum in normal weight, $P < 0.001$). OFP decreased with BMI in PCOS (46 ± 6 in obese, 52 ± 6 in overweight, and 57 ± 6% in normal weight; $P < 0.001$) and in controls (40 ± 10 in obese and 59 ± 3% in normal; $P < 0.001$). OHP in healthy obese and PCOS obese did not differ significantly, while OHP for healthy obese was increased and OFP reduced in comparison to overweight and normal weight PCOS ($P < 0.001$). Androgens did not affect OHP, OCP, and OFP.
Conclusion
PCOS was not associated with increased OHP when compared with BMI- and age-matched controls. However, increase in OHP was positively associated with BMI in PCOS and healthy women.

DOI: 10.1530/endoabs.37.EP192

EP193

PZ-TR: a novel human luciferase reporter cell line for assessment of thyroid receptor transcriptional activity

Peter Illes & Zdenek Dvorak
Department of Cell Biology and Genetics, Faculty of Science, Palacky University Olomouc, Slechtitelu 11, 783 71 Olomouc, Czech Republic.

Regulation of gene expression mediated by thyroid hormones (THs) plays an essential role in variety of physiological processes. It is known that large group of natural and synthetic compounds, generally termed endocrine disruptors, can interfere with endocrine system and thus disrupt homeostasis of hormonal regulation processes in human organism. In order to screen for substances with potential disrupting effects on TH pathway, we developed and characterized human luciferase reporter gene cell line for assessment of thyroid receptor (TR) transcriptional activity – PZ-TR. PZ-TR cell line was derived from human hepatocellular carcinoma cells HepG2, which were stably transfected with reporter plasmid containing two copies of tandem thyroid response elements (TREs) upstream of reporter gene for luciferase. Dose–response analyses showed that triiodothyronine (T_3), natural ligand of TR, induced luciferase activity in PZ-TR cells in dose-dependent manner and sensitivity of luciferase assays allowed detection of T_3 in nanomolar range of concentrations. Maximum fold induction of luciferase activity ranged from 2.5× to almost 3× after 24 h of exposure to T_3. We did not observe unspecific induction of luciferase activity by other steroid hormones and VDR ligands, only exception was partial increase of luciferase activity after treatment of PZ-TR cells with retinoic acids. Cryopreservation of PZ-TR cells did not influence their functionality, similarly responsivity to T_3 and cell morphology maintained unaffected even after long-term cultivation. Novel PZ-TR cell line was used for evaluation of effects of organic tin compounds on transcriptional activity of TR. We found that both, tributyltin derivatives and triphenyltin derivatives induced luciferase activity in PZ-TR cells. These findings indicate that organic tin compounds have potential to interfere with TR-mediated regulation of gene expression and thus influence physiological activity of THs.

This work was supported by the European Social Fund and the Ministry of Education, Youth and Sports of the Czech Republic, Project No. CZ.1.07/2.3.00/30.0004 (POST-UP).

Disclosure

This work was supported by the European Social Fund and the Ministry of Education, Youth and Sports of the Czech Republic, Project No. CZ.1.07/2.3.00/30.0004 (POST-UP).

DOI: 10.1530/endoabs.37.EP193

EP194

Evaluation of an automatic referral system for inpatients with hyponatraemia: prompt referral leads to active intervention

Jayamalathy Mannar Mannan, Mamta Joshi, Roy Vincent, Roy Sherwood, Bahram Jafar-Mohammadi, Jackie Gilbert, Benjamin Whitelaw & Simon Aylwin
King's College Hospital, London, UK.

Inpatients with hyponatraemia have a high mortality and longer length of stay. We instituted a system of automatic referral to the endocrinology team where any inpatient with a serum (Na^+) ≤125 mmol/l was referred automatically from their biochemical results.

Aims

We evaluated the diagnosis, management, and outcome of the patients referred with hyponatraemia over 6 months.

Methods

Data were prospectively captured electronically. We recorded demographics, discharge diagnoses, serum (Na^+) level, osmolalities, urinary electrolytes, thyroid function test (TFT), and cortisol status. Patients were categorised according to their initial volume status and final endocrine diagnosis. Interventions were: fluid restriction, N/Saline, hypertonic (1.8%) saline +/− furosemide or tolvaptan. Outcomes were recorded as time to sodium correction, length of stay and discharge status.

Results

61 patients were referred of whom 56 were actively managed by the endocrine team. 'True' hyponatraemia was identified in 54/56 patients. They were classified as: hypovolaemic (22.2%), hypervolaemic (25.9%), and euvolaemic (51.9%). Cortisol status was recorded or established in 81.5% and TFTs in 88.9%. Of the euvolaemic patients (28/54), 25 had SIADH-including two patients newly diagnosed with cancer; 2/28 had gluco-corticoid deficiency; one low solute intake. In patients with hypervolaemia, 42.9% were treated with fluid restriction alone and 42.9% received diuretic and hypertonic saline. 66.7% of hypovolaemic hyponatremia patients corrected with 0.9% saline alone. Amongst 25 SIADH patients, nine responded to restriction +/− drug withdrawal alone, ten were corrected with hypertonic (1.8%) saline. Glucocorticoid replacement corrected hyponatraemia in two patients. Tolvaptan was needed in four cases. Correction of sodium ((Na^+) ≥130 mmol/l) was achieved in 64.8% after a mean of 5 days.

Conclusion

Automatic referral to a specialist team from the laboratory was appropriate in >90% and led to a prompt diagnostic evaluation and active intervention.

DOI: 10.1530/endoabs.37.EP194

EP195

Klinefelter syndrome: a small sample retrospective analysis

Ana Margarida Balsa[1], Margarida Bastos[2], Carolina Moreno[2], Daniela Guelho[2], Luís Cardoso[2], Nuno Vicente[2], Diana Martins[2], Diana Oliveira[2], Márcia Alves[1], Joana Guimarães[1] & Francisco Carrilho[2]
[1]Serviço de Endocrinologia, Diabetes e Nutrição do Centro Hospitalar do Baixo Vouga, Aveiro, Portugal; [2]Serviço de Endocrinologia, Diabetes e Metabolismo do Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.

Introduction

Klinefelter syndrome (KS) is characterized by the presence of supernumerary X-chromosome and thus a 47,XXY karyotype. This syndrome remains under-diagnosed, with only about 25% of patients being identified, and only 10% during childhood.

Methods

Retrospective analysis of 11 KS patients followed-up in the Endocrinology Department of Coimbra's Hospital and Universitary Center. The registered data included education and occupation, time and motif of diagnosis, co-morbidities and treatment. Patients were divided in two groups: A – diagnosis at pediatric age, $n=8$ and B – diagnosis during adulthood, $n=3$.

Results

The mean age of diagnosis was 34.45 ± 14.2 years (A – 10.5 ± 3.1 years and B – 42.7 ± 14.2). Group A patients were diagnosed during workup of learning disabilities; on the last evaluation five had gynecomastia (62.5%) and two osteopenia (25%), none had carbohydrate metabolism disorder; they started testosterone replacement at the age of puberty; their final height was 170.3 ± 9.8 cm; four group A patients completed highschool and one couldn't read or write. One group B patient was diagnosed on account of infertility, and two on the workup of hypogonadotropic hypogonadism; on the last evaluation two had gynecomastia (66.7%), two osteopenia (66.7%), one osteoporosis (33.3%), two had psychiatric and behavioural disorders with cognitive impairment (66.7%), and two had diabetes mellitus with difficult metabolic control and proliferative retinopathy; their final height was 177.3 ± 3.8 cm. One group B patient completed highschool and had an occupation; the other two didn't finish junior high school and were unemployed.

Conclusion

Cognitive impairment was found in 90.9% of patients and was the most frequent comorbidity, with educational and professional impact. Ginecomastia and osteopenia were frequent as well. Timely diagnosis can result in a better care with proper follow-up and regular screening of possible comorbidities.

DOI: 10.1530/endoabs.37.EP195

EP196

Endocrinopathies associated with lithium therapy in an Irish tertiary referral centre

Rosemary Dineen[1], Delia Bogdanet[1], C J Thompson[1], D Thompson[1], Gerard Boran[1], James Gibney[1], Veronica Keane[1] & Mark Sherlock[2]
[1]Department of Endocrinology, Adelaide and Meath Hospital Incorporating the National Childrens Hospital, Tallaght, Dublin, Ireland; [2]Department of Pyschiatry, Adelaide and Meath Hospital Incorporating the National Childrens Hospital, Tallaght, Dublin, Ireland.

Lithium is used in psychiatric practice as maintenance therapy in bipolar disorder. It has a narrow therapeutic index with serious toxic potential. Lithium is associated with multiple endocrine and metabolic disturbances but data regarding the rates of these in individual patients is lacking. In a tertiary referral centre, all patients on lithium therapy from 2000 to 2014 were identified. The aim of this study was to assess the impact of lithium therapy on the development of endocrinopathies.
Results
Five-hundred and eighty patients were identified across the 14-year period. The median number of serum lithium measurements per person was 5 (IQR 11) with a median duration of therapy of 4.2 years (IQR 10). Toxic lithium levels were observed in 27.8% ($n=161$) of patients during follow up. Impaired renal function was more common in patients with toxic lithium levels compared to those with normal lithium levels (52.8% vs 47.2%, $P<0001$). Hypernatraemia (sodium >145 mmol/l) was observed in 16.4% of the study population ($n=95$), and it correlated with impaired renal function ($r=+0.5$, $P<0001$). 25.3% ($n=24$) of patients who had hypernatraemia also developed hyponatraemia during the follow up period. 12/29 patients assessed with hypernatremia had biochemical evidence of nephrogenic diabetes insipidus with a median plasma osmolality 295 mOsm/kg (IQR 17.75) and urine osmolality of 206.5 mOsm/kg (IQR 235).Impaired renal function was observed in 39% ($n=226$) of the study population. 30.7% ($n=178$) of patients had a TSH level >4.2 mU/l. Serum calcium was measured in 503 patients with hypercalcaemia observed in 6.4%. 4/16patients (25%) assessed for hypercalcaemia had elevated PTH level but all also had impaired renal function.
Conclusion
Chronic lithium maintenance therapy and impaired renal function were risk factors for toxicity. This study highlights the multiple electrolyte and hormone disturbances observed in patients on lithium. Clinicians should be aware of this in order to monitor, detect and institute early and appropriate management of endocrinopathies.

DOI: 10.1530/endoabs.37.EP196

EP197

The connection between serum prolactin, TSH, and insulin resistance in polycystic ovary syndrome patients

Alice Albu[1,2], Serban Radian[1], Suzana Florea[2] & Simona Fica[1,2]
[1]University of Medicine and Pharmacy Carol Davila, Bucharest, Romania; [2]Elias Hospital, Bucharest, Romania.

Introduction
Both TSH and prolactin serum levels within normal range were previously reported to be associated with metabolic parameters.
Aim
To analyse the connections between serum levels of prolactin, TSH, and insulin resistance in polycystic ovary syndrome patients.
Material and methods
322 PCOS patients (mean age 24.3 ± 5.16 years and mean BMI 28 ± 7.57 kg/m^2) with normal serum prolactin and without thyroid dysfunction evaluated between January 2007 and January 2014 were included in the study. Anthropometric, metabolic, and hormonal parameters were measured in all the patients. HOMA-IR was calculated as an index of insulin resistance.
Results
HOMA-IR was negatively correlated with serum prolactin ($P=0.001$) and positively with serum TSH ($P=0.03$) and with adiposity indices (BMI $P<0.0001$, waist $P<0.0001$, and waist:hip ratio $P<0.0001$). In multivariate linear regression both prolactin ($\beta=-0.203$, $P=0.015$) and TSH ($\beta=0.165$, $P<0.05$) were independently associated with HOMA-IR. Several models of multivariate linear regression were built with HOMA-IR as dependent variable and all the parameters associated with HOMA-IR in bivariate analysis as independent variables. In each model one of the adiposity indices (BMI, waist, or waist:hip ratios) were included in order to avoid collinearity. In these models the only independent predictor for HOMA-IR was adiposity.
Conclusion
Although, both TSH and prolactin serum levels were related to insulin resistance, this connection seems to be due to the interplay between adiposity and all these parameters in PCOS patients.

DOI: 10.1530/endoabs.37.EP197

EP198

The serum AMH/total follicle count ratio is equal in women with and without PCOS

Sverre Christian Christiansen[1,2], Tina Bjørsvik Eilertsen[3,4], Eszter Vanky[4,5] & Sven Magnus Carlsen[1,2]
[1]Unit for Applied Clinical Research, Institute for Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway; [2]Department of Endocrinology, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway; [3]Department of Obstetrics and Gynaecology, Hospital of Namsos, Nord-Trøndelag Hospital Trust, Namsos, Norway; [4]Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway; [5]Department of Obstetrics and Gynecology, St Olav's Hospital, Trondheim University Hospital, Trondheim, Norway.

Background
Anti-Müllerian hormone (AMH) has a positive linear relationship to antral follicle count (AFC) in healthy women. However, studies of intra-follicular AMH-levels indicate a non-linear relation to AFC. It is speculated whether high AMH in polycystic ovary syndrome (PCOS) women is due to overactive follicles rather than directly reflect AFC.
Study design
We used data from a previous case–control study, including 262 women with prior term (controls) and preterm births (cases) in 1999–2006. Fasting blood tests, clinical and vaginal ultrasound examination were performed. The participants were categorised to have PCOS, polycystic ovary morphology (PCOM) or to be normal controls.
Methods
PCOS was defined according to the Rotterdam criteria, PCOM was defined as having ≥12 pre-antral follicles measuring 2–9 mm in diameter, and/or increased ovarian volume (>10 ml) in at least one ovary. We analyzed AMH/AFC ratio, adjusted for age, BMI, androstenedione, free testosterone index, and insulin.
Main results
AMH had a similar linear relationship to AFC in women with PCOS, PCOM, and normal controls. Other variables included in the multivariate analysis did not change this association. The AMH/AFC ratio was similar in the three groups.
Limitations
The results apply for women who have given birth. We did not have the possibility to correct for a distribution towards either small follicles (>2 mm) or larger follicles (<9 mm).
Implications of the findings
AMH seems to be a reliable predictor of AFC independent of PCOS diagnosis or ovarian morphology. AMH can be used as a substitute indicator of AFC in most women of fertile age.

DOI: 10.1530/endoabs.37.EP198

EP199

Endocrine emergencies as problem in Emergency Department 6 years observation including over 200 000 admissions

Krzysztof Marczewski[1,2], Michal Slomian[1,2], Dorota Boniek-Poprawa[1,2] & Marek Maciejewski[1,2]
[1]Pope John Paul II Regional Hospital, Zamosc, Poland; [2]Zamosc University of Management and Administration, Zamosc, Poland.

Introduction
Emergencies in endocrinology often require a doctor's high-speed operation, which is closely related to the ability to fast obtain a diagnosis. To remain a champion requires exercise. Therefore, we decided to check how often the doctors in the Emergency Department (ED) meet such patients.
The aim of our study was to investigate the frequency of endocrine emergencies in Department of Emergency in Tertiary Care Hospital with Department of Endocrinology.
Results
In 6 years from 16th Jul 2006–15th Jul 2012 to our ED was sent or came 200 954 patients (100 727 women). From this patients 40% was sent for treatment to other departments of the hospital and 60% were treated only in the ED. Among these 120 506 patients, endocrine emergency as the main diagnosis was established in 1100 (0.9%) patients. Among patients with endocrine emergencies, the vast majority were diabetes ($793=0.66\%$) and thyroid diseases ($128=0.11\%$). For the remaining 179 (0.15%) patients, ED doctors established 28 different diagnoses, including seven diagnoses identified in only one patient. This means that the ED

doctors treated this patient approximately every 12 days as one of the 55 patients with other diseases. Among patients referred for treatment to other departments of the hospital with indications of endocrine emergencies only diabetes occurred relatively frequently.
Comments
We cannot exclude that part of the endocrine diseases was undiagnosed or not given as the main diagnosis. The majority of our endocrine patients are admitted elective mainly from the specialised outpatient clinics or family physicians.
Conclusion
Endocrine emergencies except diabetes and thyroid diseases are rare or very rare diseases and their diagnosis is a challenge for ED physicians. Very important, therefore, seems to be good cooperation between ED and Endocrinology Department.

DOI: 10.1530/endoabs.37.EP199

EP200

ThyrART: association of embryo quality and reproductive outcome after IVF with thyroid autoimmunity

Gesthimani Mintziori[1], Efstratios M Kolibianakis[1], Aristidis Slavakis[2], Basil C Tarlatzis[1] & Dimitrios G Goulis[1]
[1]Units of Reproductive Endocrinology and Human Reproduction, First Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, Thessaloniki, Greece; [2]Hormone Assay Laboratory, Department of Biochemistry, Hippokration Hospital, Thessaloniki, Greece.

Introduction
The role of thyroxine (T_4) during embryo development is recognised as crucial. The research question of this study was if embryo quality and reproductive outcomes after IVF are affected by maternal thyroid function and/or thyroid autoimmunity (TAI).
Methods/design
We conducted a prospective study (ThyrART), assessing embryo quality and reproductive outcome of women undergoing ovarian stimulation with a flexible GnRH-antagonist protocol for IVF (classic or ICSI), whose thyroid function (TSH, fT_3, and fT_4) and TAI (anti-TPO and anti-Tg) were closely observed. Embryo quality scores were calculated and reproductive outcomes were recorded.
Results
Best embryo score at day 2 was positively correlated with the overall change of fT_4 concentrations ($r=0.64$, $P=0.048$). Biochemical pregnancy and live birth rates were negatively correlated with overall change of TSH concentrations ($r=-0.741$, $P=0.004$ and $r=-0.534$, $P=0.06$ respectively).
Conclusion
The facts that changes in maternal TSH concentrations are associated with pregnancy outcomes and that changes in thyroid hormones are associated with embryo parameters need further confirmation. Interventional studies in women undergoing ovarian stimulation for IVF are needed to demonstrate a possible positive influence of levo-thyroxine supplementation, in selected cases, on their reproductive outcomes.
Disclosure
This work was supported by Hellenic Endocrine Society (research grant).

DOI: 10.1530/endoabs.37.EP200

EP201

Association of rs1800790 in fibrinogen beta polypeptide chain gene (FGB) with endometrium in Iranian women

Zohreh Omidi[1] & Ahmad Ebrahimi[2]
[1]Department of Medical Genetics, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran; [2]Cellular and Molecular Research Center, Obesity Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Background
Endometriosis is a common disease in women and considered as one of the most important reasons infertility, and it means abnormal growth of the endometrial tissue outside of the uterine. The exact prevalence of endometriosis disease is unknown. estimated that the endometriosis exists in 10% of women in productivity. Possibly, several genes interacting with each other as well as environment to result endometriosis. Given that one of the cellular pathways involved in endometriosis coagulation is since beta fibrinogen level rise increases the fibrin and it is an increasing cause of venous thrombosis? association of this gene and gene polymorphism FGB-455 (rs-1800790) was examined in Iranian women.
Materials and methods
After isolation of genomic DNA from the blood lymphocytes, assessing of this polymorphism was conducted by using TETRA ARMs–PCR method in 100 endometriosis patients and 100 control individuals.
Results
FGB gene polymorphism genotype frequencies were compared in the patients and control individuals. Abundance of AA, AG, and GG genotypes of the gene polymorphism FGB were 28, 48, and 24% in patients respectively, and 66, 31, and 3% in control group respectively. Results showed that there is meaningful relation between patients and control group ($P=4.619\times10^{-11}$).
Conclusion
Our findings showed that there was significant relationship between *FGB* gene polymorphism and increased risk of endometriosis in women studied. Therefore can be a determining predictive molecular biomarker identification faster and better treatment of endometriosis should be used.

DOI: 10.1530/endoabs.37.EP201

EP202

A haplotype of the *EPCR* gene is associated is a candidate risk factor for uterine myomas in Iranian women

Zeinab Fathkhani[1] & Ahmad Ebrahimi[2]
[1]Department of Medical Genetics, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran; [2]Cellular and Molecular Research Center, Obesity Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Introduction
Uterine myomas are the most frequent benign uterine tumours of smooth muscle cells of myometrium. Myoma is the most common uterine tumours occurring in 20–30% of women during their reproductive years. Despite this common complication of benign tumours, in most cases there are barrier of natural fertility and pregnancy continuing. Therefore, to understanding better the genetic characteristics of myoma help us in the treatment and preventive measures in these cases. The protein product of the *EPCR* gene activates a part of the protein C anti-coagulation pathway. The purpose of this study is to examine EPCR 4600A>G (A3 haplotype) and its relationship with uterine myoma in affected Iranian women with myoma.
Methods
In this case–control study, 100 women with myoma and 100 healthy women were studied as controls and genotype distribution of polymorphism in *EPCR* gene was investigated through tetra-ARMS-PCR method and the test results were analysed using χ^2 test.
Results
EPCR gene polymorphism (rs867186) genotype frequencies were compared in the patients and control groups; the frequency of AA, AG, and GG genotypes were 19, 78, and 3% in the patients group and 37, 43, and 20% in the control groups respectively. Results showed that there was no significant difference between patients and control group ($P=0.9$).
Conclusion
The results of present study revealed that there is a possible association between the presence of C allele in *EPCR* gene polymorphism (rs867186) and risk of uterine myoma in Iranian population and suggests this variation as a predictor marker for estimating the risk of uterine myoma.

DOI: 10.1530/endoabs.37.EP202

EP203

Sexual function in women with polycystic ovary syndrome

Justina Sematonyte[1], Vilija Danylaite[2], Lina Ciaplinskiene[2], Dalia Kozloviene[2], Audrone Sebokaite[2], Malvina Pagareckaite[1] & Birute Zilaitiene[2]
[1]Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania; [2]Institute of Endocrinology, Lithuanian University of Health Sciences, Kaunas, Lithuania.

Objective
Polycystic ovary syndrome (PCOS), is a common endocrine disorder in women of reproductive age, which influences metabolic, psychological and sexual aspects of their life. We aimed to evaluate the sexual function of women with PCOS in comparison with age-matched controls.
Methods
In this prospective cross-sectional study, 40 women with PCOS (mean age 27.02 ± 4.54 years) were compared with a control group of 40 healthy volunteers (mean age 25.28 ± 4.37 years). All women used barrier contraception methods at the enrolment into the study. The degree of hirsutism was assessed using the modified Ferriman–Gallwey scale. Subjects' sexual function was evaluated using the female sexual function index (FSFI). Women were considered to be at risk for sexual dysfunction in the case of FSFI score $\leq$26.55. Testosterone and SHBG concentrations were measured by RIA Kits (DIA Source, Belgium).
Results
Mean FSFI score in women with PCOS was 24.89 ± 10.61, in the control group 24.71 ± 7.16 ($P=0.498$). There were no differences in the FSFI domains scores between groups as well. 65% ($n=26$) of women in PCOS and 65% ($n=26$) in the control group were at risk for sexual dysfunction ($P=0.946$). Non-obese PCOS women reported higher FSFI scores than obese women with PCOS ($P=0.041$). FSFI scores in PCOS patients with amenorrhea ($\leq$3 menstrual cycles/year) were lower if compared with patients with oligomenorrhea (4–8 cycles/year), $P=0.045$. Neither testosterone concentration nor hirsutism score were related to the sexual function of the study subjects.
Conclusions
The sexual function in women with PCOS did not differ from their age-matched healthy counterparts. A high percentage of young Lithuanian women are at risk for sexual dysfunction independently of their androgen status. Clinical features of PCOS might determine sexual function in PCOS patients.

DOI: 10.1530/endoabs.37.EP203

EP204

Salivary cortisol response to psychological stress in late adolescent and young women: impact of menstrual irregularity, hirsutism, and hyperandrogenaemia

Marco Mezzullo, Alessandra Gambineri, Flaminia Fanelli, Andrea Repaci, Olga Prontera, Guido Di Dalmazi, Uberto Pagotto & Renato Pasquali
Endocrinology Unit, Department of Medical and Surgical Science, Center for Applied Biomedical Research, S.Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy.

Hyperandrogenic disorders cause psychological implication in young girls, limiting the quality of life. Salivary cortisol (SalF) testing was proved to be useful in the evaluations of acute stress responses. Aim of this study was to investigate SalF responses to a stressor event in late adolescent females. We selected 165 drug-free females aged 16–19 years from a cross-sectional epidemiological study. Saliva was collected in the morning before and after a stressor event consisting in a physical examination by a trained physician for anthropometric data collection and hirsutism scoring and in a structured interview about familiar and menstrual history. Blood was collected for biochemical and hormonal evaluation. SalF and serum total testosterone (TT) were assessed by liquid chromatography–mass spectrometry. Subjects were subdivided in: menstrual irregularities group (MI, $\leq$10 bleeding/year; $n=27$), isolated hirsutism group (IH, modified Ferriman–Gallwey score $\geq$8; $n=37$), isolated hyperandrogenaemia group (IHA, TT> age/menstrual phase-specific cut-off; $n=11$), and normal controls (NC; $n=90$). Glucose, insulin, and lipid profile were normal and non different among groups. Compared to NC (21.2 ± 0.3 kg/m^2), IH (22.4 ± 0.52 kg/m^2, $P=0.0169$) and IHA (23.5 ± 0.77 kg/m^2, $P=0.004$) displayed higher BMI; IHA also displayed higher waist circumference (75.4 ± 0.71 cm vs 81.0 ± 2.3 cm, respectively, $P=0.015$). Compared to NC, IH had lower SHBG (48.11 ± 1.75 nmol/l vs 42.7 ± 2.96 nmol/l, respectively, $P=0.039$). Basal SalF was not different among groups ($P=0.977$); a significant SalF increase after the stressor event was observed only in ICH (1.21 ± 0.15 ng/ml vs 1.67 ± 0.23 ng/ml, $P=0.029$). SalF relative increase (dSalF%) was significantly different among groups ($P=0.015$); in particular, dSalF% was significantly higher in ICH compared to NC (56.1 ± 18.2% vs 3.4 ± 5.1%, respectively, $P=0.010$), and this data was confirmed after adjustment for BMI, SHBG, and waist circumferences ($P=0.0051$). We conclude that hirsutism, major feature of clinical hyperandrogenism but not mestrual irregularities nor hyperandrogenaemia, plays a major role in the responsiveness to stress as measured by SalF in young girls.
Disclosure
This research received an unrestricted grant from a not-for-profit Foundation 'Fondazione Centro Studi sulla Calvizie Cesare Ragazzi Laboratories', Zola Pedrosa Bologna Italy; this work was also supported by the Emilia-Romagna Region University.

DOI: 10.1530/endoabs.37.EP204

EP205

Leptin and insulin resistance: impact on gonadal function in Algerian obese women

Djida Remini[1], Aziza Smili[1], Djamila Meskine[2], El Hadj Ahmed Koceir[3] & Yacine Soltani[1]
[1]Laboratory of Biology and Physiology of Organisms, Endocrinology Team, Faculty of Biological Sciences, USTHB, Algiers, Algeria; [2]Department of Endocrinology, IBN ZIRI Hospital, Bologhine, Algiers, Algeria; [3]Laboratory of Biology and Physiology of Organisms, Bioenergetic and Intermediate Metabolism Team, Faculty of biological Sciences, USTHB, Algiers, Algeria.

Introduction
Excess of abdominal fat may disturb metabolic parameters that affect insulin level and may lead to menstrual disorders, consecutively to disturbance in sex steroids production. The aim is to link the metabolic hormones in abdominal obesity, with reproductive axis hormones in women at age.
Patients and methods
85 no menopausal women aged between 17 and 52 were recruited: 62 with abdominal obesity (BMI >30 kg/m^2 and waist circumference >80) and 23 normal weight for controls (BMI <25). Lipidemia, fasting plasma glucose, insulin, leptin, adiponectin, LH, FSH, oestradiol (in follicular phase), progesterone (in luteal phase), 17OHP, SDHEA, total and free testosterone using free androgen index (FAI), and sex hormone binding globulin (SHBG) were analysed. Insulin resistance and sensitivity were estimated by HOMA-IR and QUIKI indexes.
Results
Obese women show ovulation disorders (52%) type spaniomenorrhea sometimes up to amenorrhea, hirsutism (50.79%), acne (25.4%) associated to high leptin (60.91%, $P<0.001$), cholesterol (17.32%, $P=0.00017$), triglycerides (38.98%, $P=0.00014$), LDL-c (18.80%, $P=0.0014$), decreased HDL-c (17.02%, $P=0.0085$), and insulin resistance (HOMA: 10.11 vs 4.39) due to decreased insulin sensitivity (QUIKI: 0.68 vs 0.83). The high levels of FSH (32.89%, $P=0.0495$), oestradiol (11.18%, $P=0.46$), LH (16.93%, $P=0.349$), total and free testosterone (15%, $P=0.23$), and FAI (20.42%), were associated to significant rise of leptin (68.69%, $P=0.001$), slight decrease of adiponectin reduced both progesterone (64.22%, $P=0.0003$), 17OHP (24.34%, $P=0.18$), and DHEAS (8%, $P=0.587$) as well as circulating SHBG (11.83%, $P=0.38$).
Conclusion
Insulin resistance and dyslipidaemia in obese women may contribute to increase aromatase activity and decrease liver SHBG production which led to increase total and free plasma testosterone, whereas the rise of plasma gonadotropins should be consecutive to the stimulating effect of leptin on LHRH neurons. According to clinical thresholds, our results may suggest the occurrence of hyperandrogenism in obese women, but not associated with polycystic ovary syndrome.
Disclosure
This work was supported by financial gift from the Algerian National Research Program (PNR).

DOI: 10.1530/endoabs.37.EP205

EP206

PCOS and thyroid disorder

Samia Ould Kablia, Aicha Lechghem & Assya Cheikh
Central Hospital of the Army, Algiers, Algeria.

Background
PCOS and thyroid disorder are two of the most frequent endocrine disorder in the general population. Although, the aetiopathogenesis of thyroiditis and PCOS is completely different this two entities have many features in common (cystic ovaries in hypothyroidism and thyroid disorder in PCOS).

Objective
Our objective was to assess the increased incidence of thyroid disorder in females with PCOS.
Methods and materials
We conduct a prospective study from 2005 to 2012, 150 PCOS and 80 controls were enrolled. All patients were screened for TSH, TPO antibodies, and a clinical exam of the neck.
Results
PCOS and controls were matched for age and BMI. The mean BMI was 27.2 kg/m^2 and the mean age 24.5 years. The thyroid disorders were more frequent in PCOS (8.66%) than in controls (1.25%). two goitres, nine thyroiditis, and two infraclinical hypothyroidism (TSH >4.5 UI/ml) were found in PCOS women. The TPO antibodies were positive in 6% of them and the mean level = 250 UI/ml.
Discussion
In our study thyroid disorders are more frequent in PCOS women than in controls, however the prevalence (8.66%) is quite similar to the general population. Increased BMI, insulin resistance, hyperostrogenemia, proinflammatory markers are thought to be the link between this two disorders.
Conclusion
There is enough literature report to argue that prevalence thyroid disorders is increased in PCOS women. The link between this two disorders is not elucidated.

DOI: 10.1530/endoabs.37.EP206

EP207

Biochemical and hormonal parameters in patients presenting with hirsutism

Yildiz Okuturlar[1], Samet Sayilan[1], Meral Mert[2], Ozlem Soyluk[2], Ezgi Erdogan[1], Ozlem Harmankaya[1] & Abdulbaki Kumbasar[1]
[1]Department of Internal Medicine, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey; [2]Department of Endocrinology and Metabolism, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey.

Introduction
It was aimed to evaluate the biochemical and hormonal parameters in female patients with and without polycystic ovary and presenting with symptoms of hirsutism.
Materials and methods
In this study, 217 female patients presenting with symptoms of hirsutism were enrolled. Seventy-two female patients having polycystic ovaries by ultrasonography were named as group 1 and 145 female patients with normal ovaries were named as group 2. FSH, LH, plasma total and free testosterone, DHEA-S, 17-hydroxyprogesterone (17-OH Prog), glucose, homeostasis model assessment (HOMA-IR), HbA1c, total cholesterol, triglyceride, LDL cholesterol (LDL-C), and HDL cholesterol (HDL-C) were recorded.
Results
While there was statistically significant difference between total testosterone (0.62 ± 0.26, 0.56 ± 0.24) and LH/FSH ratio (1.54 ± 1.21, 1.18 ± 0.92) in groups 1 and 2 ($P = 0.09$ in both), there were no differences among the values of free testosterone, LH, FSH, 17-OH Prog, and DHEA-S. There were no significant differences in lipid profile, glucose, insulin, HOMA-IR, HbA1c, and plasma uric acid levels. While there were positive correlations between HbA1c and total testosterone, free testosterone and HOMA-IR, HbA1c and insulin in group 1, there were negative correlations between LDL-C and total testosterone, HDL-C and free testosterone in group 2. There was a positive correlation between HOMA-IR and insulin in LH/FSH ratio only in group 2.
Conclusion
Hirsutism cases should be closely monitored in terms of metabolic parameters and cardiovascular risk factors. While evaluating hormone profile in these patients, it may be appropriate to conduct research in terms of glucose metabolism disorders and dyslipidaemia.

DOI: 10.1530/endoabs.37.EP207

EP208

An endocrine disrupting chemical, bisphenol A: could it be associated with sex differentiation in brain regarding to transsexuality?

Banu Sarer Yurekli, Nilufer Ozdemir Kutbay & Fusun Saygili
Endocrinology Department, Faculty of Medicine, Ege University, Izmir, Turkey.

Transsexuality is characterised by a belief of having been born in a wrong body. Sexual differentiation of genitals take place in the first 2 months of pregnancy. Sexual differentiation of brain takes place in the second half of pregnancy. It is found that there is structural sex differences in the central nucleus of the bed nucleus of the stria terminalis (BSTc). Structural differences were found to be reversed in transsexual people. In humans main mechanism appears to involve a direct effect of testosterone on the developing brain. Direct effect of testosterone on developing brain in boys and lack of this effect in girls are crucial factors in the development of male and female gender identity. The origin of transsexuality is based on the fact that the differentiation of sexual organs takes place before the sexual differentiation of the brain. It was found a reversal in BSTc. In men this area is twice the size of that in women. In male-to-female transsexuals they found female BSTc. They had shown that sex reversal of the differences in the BSTc were independent of changing hormone levels in adulthood. The size of BSTc and the number of neurons match the gender that transsexuals feel they belong to, not the sex of their sexual organs. An endocrine disrupting chemical (EDC), bisphenol A (BPA), acts as oestrogen mimic compund. BPA may affect sexual differentiation of brain and cause reversal of differentiation in male to female transsexual as female brain. Brain expresses the oestrogen receptors and other hormone receptors making it a potential target for EDC. Transsexuality presume a combination of a genetic background and an early effect on interaction of sex hormones with developing brain during critical foetal period. We hypothesize that exposure to BPA may be a cause for transsexualism.

DOI: 10.1530/endoabs.37.EP208

EP209

The commonly used plasticisers (bisphenols and phthalates) as endocrine disrupting chemicals in healthy women and women with polycystic ovary syndrome

Aleksandra Rutkowska[1], Aleksandra Konieczna[1], Kamila Wilczewska[2], Agnieszka Ciechanowicz[2], Radoslaw Czernych[4], Agnieszka Kowalewska-Wlas[5], Lukasz Laczmanski[3], Justyna Kuliczkowska[3], Agnieszka Lenarcik[3], Anna Trzmiel-Bira[3], Anna Brona[3], Monika Kuligowska-Jakubowska[1], Agata Kot-Wasik[2], Andrzej Wasik[2], Andrzej Milewicz[3], Jacek Namiesnik[2], Lidia Wolska[4] & Dominik Rachon[1]
[1]Department of Clinical and Experimental Endocrinology, Medical University of Gdansk, Gdansk, Poland; [2]Department of Analytical Chemistry, Gdansk University of Technology, Gdansk, Poland; [3]Department and Clinic of Endocrinology, Diabetology and Isotope Therapy, Medical University of Wroclaw, Wroclaw, Poland; [4]Department of Environmental Toxicology, Medical University of Gdansk, Gdansk, Poland; [5]Independent Specialist of Gynaecology, Gdansk, Poland.

Plasticisers such as bisphenol A (BPA), bisphenol S (BPS), and phthalates (PAE) are commonly used in daily life in electronic equipment, cans, plastic food containers, and bottles. These substances can interact with oestrogen receptors as well as androgen receptors and therefore they are called endocrine disrupting chemicals (EDC). The aim of this study was to evaluate serum concentrations of BPA, BPS, and selected PAE in healthy women and women with polycystic ovary syndrome (PCOS). In total 191 women were studied. Eighty-six patients were diagnosed with PCOS according to the ESHRE/ASRME criteria. The healthy group consisted of 105 women without any endocrinopathies and not taking any hormonal contraceptives. Serum levels of prolactin, LH, FSH, 17OH-progesterone, total testosterone, DHEAS, insulin, and sex hormone binding globulin were measured. BPA and BPS concentration were analysed in all women's sera using high pressure liquid chromatography method combined with mass spectrometry. Phthalates concentration were identified in biological samples using gas chromatography. Serum concentration of plasticisers were detected in 35% of samples for BPS and 90% of samples for BPA and PAEs respectively. The results of the analysis have pointed also to the higher levels of BPA in the sera of women with PCOS in comparison with healthy controls. There has been a strong positive correlation between serum concentrations of BPA and BPS with free androgen index and negative correlation with serum oestradiol level. Summarising, the results for plasticisers' concentrations and their impact on the hormonal profile confirm their endocrine disrupting potential.
Disclosure
This work was partially supported by Polish Ministry of Science – grant number 01-0156/08.

DOI: 10.1530/endoabs.37.EP209

EP210

Serum gonadotropins secretion is not reduced with advancing age in HIV-infected females: results of a case–control study in menopausal women

Chiara Diazzi[1,2], Giulia Brigante[1,2], Giovanni Guaraldi[3], Manuela Simoni[1,2] & Vincenzo Rochira[1,2]
[1]Unit of Endocrinology, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy; [2]Azienda USL of Modena, Modena, Italy; [3]Metabolic Clinic, Infectious and Tropical Diseases Unit, Department of Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia, Modena, Italy.

Introduction
HIV infection treated with highly active antiretroviral therapy (HAART) seems to be associated with hypogonadism in men. Less is known in HIV-infected women gonadal status. The aim of this study is to investigate gonadal function, in menopausal HIV-infected women compared sex- and age-matched healthy subjects (HS).
Methods
We retrospectively compared 188 HIV-infected women with 192 HS selected reviewing record charts and laboratory database respectively. We considered only women older than 50 years and we grouped them according to their age (50–54; 55–59; and >60 years). Basal serum LH, FSH, estradiol, and testosterone were measured. The FSH cut-off of 40 UI/l for establishing menopausal status.
Results
The percentage of subjects with FSH levels >40 UI/l was higher in HIV-infected women (67.5%) than in healthy controls (59.4%). This difference was found also in the younger subgroup (38% vs 27%). FSH serum levels in HIV-infected women (54.08±31.47 mUI/ml) did not differ ($P=0.27$) from HS (50.87±31 mUI/ml). Accordingly, no significant differences were found in LH, estradiol, and testosterone levels.
Conclusions
Menopause seems to occur at a younger age than HS in HIV-infected women. Moreover, differently from what was documented in HIV-infected male counterpart, HIV-infected women seem to not develop hypogonadotropic hypogonadism, but have a tendency to higher serum FSH at a younger age (<54 years) suggesting premature hypergonadotropic hypogonadism. With this in view menopause may be considered an element of the process of premature aging associated with HIV infection and its comorbidities.

DOI: 10.1530/endoabs.37.EP210

EP211

Association between Apa-I polymorphism in the vitamin D receptor gene and metabolic syndrome in polycystic ovary syndrome

Betânia R Santos[1,2] & Poli Mara Spritzer[1,2]
[1]Gynecological Endocrinology Unit, Division of Endocrinology, Hospital de Clinicas de Porto Alegre, Porto Alegre/RS, Brazil; [2]Federal University of Rio Grande do sul, Porto Alegre/RS, Brazil.

Women with polycystic ovary syndrome (PCOS) have higher prevalence of metabolic disturbances such as changes in lipid profile, diabetes, hypertension and metabolic syndrome. Variants on vitamin D receptor (VDR) gene have also been related to metabolic comorbidities in general population. Therefore, the aim of the present study was to investigate whether Apa-I polymorphism (rs7974232) in the VDR gene is associated with metabolic syndrome and endocrine profile in PCOS. In this cross-sectional study 190 PCOS (Rotterdam criteria) and 100 non-hirsute and ovulatory control women were enrolled. Endocrine and clinical measurements were assessed and genotypic analyses were evaluated by real time PCR. PCOS women were younger (22.9±6.7 vs 25.2±7.7 years; $P=0.013$) and had significantly higher BMI (29.7±6.4 vs 27.0±6.1 kg/m^2; $P=0.001$), total testosterone (0.90±0.40 vs 0.54±0.17 ng/ml; $P<0.001$) and fasting insulin (16.87 (9.81–26.97) vs 11.09 (7.34–15.44); $P<001$). Metabolic syndrome was present in 26.5% of PCOS and in 4.8% of controls. The genotypic distribution for Apa-I SNP in PCOS (AA: 32.1%%, AC: 46.3%, CC: 21.6%) and controls (AA: 36.0%%, AC: 48.0%, CC: 16.0%) was similar. PCOS participants with the CC genotype (CC vs CA+AA) of Apa-I had higher risk for metabolic syndrome (OR: 2.133; 95% CI 1.020–4.464, $P=0.042$). While the analyses among control participants showed that metabolic syndrome is more frequent in CC that CA+AA genotype (13.3% vs 2.9%), no significance was found, (OR: 5.154; 95% CI 0.665–39.954, $P=0.145$), maybe because of the low prevalence of metabolic syndrome in this group. The CC genotype was also associated with higher systolic blood pressure ($P=0.009$), total cholesterol ($P=0.040$) and LDL ($P=0.038$) in both PCOS and control groups (ANOVA two-way). In conclusion, the present results suggest that variant Apa-I in VDR gene may be associated with metabolic syndrome in women with PCOS.
Disclosure
This work was supported by grant from CNPq INCT 573747/2008-3, Brazil.

DOI: 10.1530/endoabs.37.EP211

EP212

XbaI and PvuII oestrogen receptor alpha gene polymorphism and Y chromosome deletions in infertile vs fertile men

Suzana Vladoiu[1], Dana Dinu[1], Gabriela Anton[2], Anca Botezatu[2], Dana Manda[1], Sabina Oros[1], Olga Ianas[1], Diana Paun[1], Corin Badiu[1] & Roxana Rosca[1]
[1]C.I.Parhon National Institute of Endocrinology, Bucharest, Romania; [2]Stefan S. Nicolau Institute of Virology, Bucharest, Romania.

Only a few genes involved in spermatogenesis have clinical importance: Y chromosome micro deletions in the region called azoospermia factor (AZF) and oestrogen receptor alpha gene polymorphisms (ESR1).
Objective
The study aim to evaluate ESR1 and Y chromosome deletion in infertile men.
Subjects and methods
43 infertile men, and 34 fertile men aged 20–50 years 50, were enrolled after signing the informed consent. Screening for microdeletions in the azoospermia factor (AZF) region of Y chromosome was performed by multiplex PCR and oestrogen receptor alpha (ESR1) gene polymorphisms XbaI and PvuII was performed by RFLP.
Results
In infertile patients ESR XbaI polymorphism 15 cases were wild type homozygote (XX), 23 heterozygote (Xx) and four mutant homozygote (xx). The frequency of x allele was 0.37, and 0.63 for X allele, $\chi^2=1.299$. In normal patients ESR XbaI polymorphism 14 cases were homozygote for normal allele (XX), 17 were heterozygote (Xx) and three were mutant homozygote (xx). The frequency of x allele in population was 0.34, for X allele the frequency was 0.66, $\chi^2=0.464$. In infertile patients ESR PvuII polymorphism 12 cases were homozygote (PP), 22 were heterozygote (Pp) and eight were mutant homozygote (pp). The frequency of p allele was 0.45, and 0.55 for P allele, $\chi^2=0.137$. In normal patients ESR PvuII polymorphism ten cases were homozygote for normal allele PP), 18 were heterozygote (Pp) and six were mutant homozygote (pp). The frequency of p allele was 0.44, for P allele the frequency was 0.56, $\chi^2=0.184$. 6.97% of all patients presented microdeletions in AZFc region and 2.32% in AZFb region, 6.97% in AZFb and AZFc regions.
Conclusion
For the two ESR1 studied polymorphism the investigated group is in HW equilibrum. No significant differences were found between the mutant allele's frequency between the infertile patients and the control group.
Disclosure
Acknowledgement: This work received financial support through the project entitled 'CERO – Career profile: Romanian Researcher', grant number POSDRU/159/1.5/S/135760, co-financed by the European Social Fund for Sectorial Operational.

DOI: 10.1530/endoabs.37.EP212

EP213

The impact of adiposity on serum anti-Mullerian hormone in normal and overweight women with decreased ovarian reserve

Dragos Albu, Raluca Tulin & Alice Albu
University of Medicine and Pharmacy Carol Davila, Bucharest, Romania.

Background
Few previous studies suggested a negative impact of obesity on anti-Mullerian hormone (AMH) serum levels in patients with decreased ovarian reserve, but the data regarding the relationship between AMH and adiposity in the same category of patients without severe excess of body weight are scarce.
Aim
The aim of the study was to evaluate the relationship between AMH serum levels and BMI in normal weight and overweight patients with reduced ovarian reserve.
Material and methods
Patients were 196 infertile women with reduced ovarian reserve defined as AMH $\leq$ 1 ng/ml evaluated in a Department of Assisted Reproduction between January 2007 and January 2014. Inclusion criterion was BMI $\leq$ 30 kg/m^2. Weight, height, age were recorded and AMH was measured in all the patients.
Results
Mean age of the study group was 36.9 $\pm$ 4 years and mean BMI 21.8 $\pm$ 2.8 kg/m^2 (170 normal weight patients and 26 overweight patients). Serum AMH was negatively correlated with age ($r = -0.154$, $P < 0.05$) and BMI ($r = -0.147$, $P < 0.05$) when the entire group was analyzed, but the correlation was lost when only normal weight women were included in analysis. In a multivariate linear regression model both age ($P < 0.0001$) and BMI ($P = 0.017$) were independently associated with serum AMH.
Conclusion
We found that in women with decreased ovarian reserve there is a negative impact of only slightly increased adiposity on serum AMH and this effect is independent of age.

DOI: 10.1530/endoabs.37.EP213

EP214

Clinical characteristics of different phenotypes of polycystic ovary syndrome

Tamara Bogavac[1], Djuro Macut[1], Ivana Bozic Antic[1], Jelica Bjekic-Macut[2], Danijela Vojnovic Milutinovic[3], Bojana Popovic[1], Biljana Kastratovic-kotlica[4], Dusan Ilic[1], Tatjana Isailovic[1], Valentina Elezovic[1], Sanja Ognjanovic[1] & Svetozar Damjanovic[1]
[1]Clinic of Endocrinology, Diabetes and Metabolic Diseases, Belgrade, Serbia; [2]CHC Bezanijska kosa, Belgrade, Serbia; [3]IBISS, University of Belgrade, Belgrade, Serbia; [4]Clinic of Gynecology and Obstetrics, Belgrade, Serbia.

Introduction
Although phenotype D is well recognised in clinical studies about PCOS, there is still a debate if this phenotype should be evaluated as part of PCOS spectrum. The aim of this study was to evaluate usual anthropometric characteristics in PCOS phenotypes.
Methodology
We evaluated 365 PCOS women (PCOS: 25.05 $\pm$ 6.24 kg/m^2; 25.48 $\pm$ 5.21 years) diagnosed using ESHRE/ASRM criteria and 125 BMI-matched healthy women (Controls: 25.41 $\pm$ 5.16 kg/m^2; 30.35 $\pm$ 5.62 years). PCOS group was divided into four phenotypes: a (anovulation (ANOV), hyperandrogenism (HA), polycystic ovary morphology (PCOM)), B (ANOV, HA), C (HA, PCOM) and D (ANOV, PCOM) and analyzed for menarche age, number of menstrual cycles/year, mean diameter of the ovaries measured by the ultrasound, and degree of hirsutism assessed by Ferriman–Gallway score.
Results
Phenotype C had the same mean number of menstrual cycles per year as Controls (11.39 $\pm$ 1.18 vs 11.74 $\pm$ 0.96, $P > 0.05$) and significantly more than all other phenotypes (A: 5.62 $\pm$ 3.49, B: 7.24 $\pm$ 4.27, D: 6.82 $\pm$ 3.39, $P < 0.05$). Menarche started significantly ($P < 0.05$) later in phenotype A and D (12.94 $\pm$ 1.69 and 13.09 $\pm$ 1.12 years, respectively) in comparison to phenotypes B, C and Controls (12.51 $\pm$ 1.26, 12.59 $\pm$ 1.40 and 12.52 $\pm$ 1.36 years, respectively). Ovaries were significantly smaller ($P < 0.05$) in phenotype B and Controls (28.79 $\pm$ 7.09 and 27.93 $\pm$ 5.73 mm, respectively, $P > 0.05$) than phenotypes A (33.13 $\pm$ 5.29 mm), C (31.94 $\pm$ 4.76 mm) and D (32.76 $\pm$ 3.89 mm). Degree of hirsutism was the same in phenotype D and Controls (3.24 $\pm$ 2.50 and 3.73 $\pm$ 2.23, $P > 0.05$) and was significantly ($P < 0.001$) lower than in all other phenotypes (A: 9.99 $\pm$ 6.13, B: 10.33 $\pm$ 4.73 and C: 11.64 $\pm$ 5.66, $P > 0.05$).
Conclusion
Our results showed that assessed clinical characteristics (menstrual frequency and degree of hirsutism) are in relation to the mainly hyperandrogenic phenotypes while it was not a case for the ovarian characteristics.

DOI: 10.1530/endoabs.37.EP214

EP215

Effects of oral contraceptives on the periodontium

Ioana Virtej[1,2], Theodoros Ikonomou[3], Anca Virtej[4], Petrache Vartej[5] & Catalina Poiana[2]
[1]Endocrine Private Practice, Trikala, Greece; [2]Department of Endocrinology, University of Medicine, Bucharest, Romania; [3]Orthodontic Private Pratice, Trikala, Greece; [4]Department of Biomedicine, University of Bergen, Bergen, Norway; [5]Department of Obstetrics and Gynecology, University of Medicine, Bucharest, Romania.

Gingivitis is the most frequent periodontal manifestation during oral contraceptives therapy, mainly due to the altered oral bacterial flora under the influence of oestrogen and progesterone. The aim of this study was to investigate the influence of low-dose oral contraceptives on periodontal health in young females.
Methods
42 women aged 18–38 years without systemic disease, non-smokers, were divided in two study groups: 22 women treated with low-dose oral contraceptives (OC) for 12 months and a control group of 20 women not using OC. Periodontal assessment included gingival index, probing depth, and attachment level at six sites per tooth. The OC users were examined before, at 6 and 12 months of therapy. The gingival index was appreciated as normal (Score 0), minimal (Score 1), moderate (Score 2) or severe (Score 3) depending on gingival colour, vascularisation, oedema, bleeding, ulceration.
Results
Pretreatment 72% had normal gingival aspect (Score 0) and 28% had a Score 1. The percentage of patients with moderate gingivitis (Score 2) was 42% at 6 months and 75% at 12 months. A severe gingival index (Score 3) was noted only at 12 months in 18% of cases. OC users at 12 months had higher gingival index scores, deeper mean probing depths (3.7 mm vs 2.4 mm; $P = 0.01$) and more severe attachment loss (2.4 mm vs 1.5 mm; $P = 0.015$) compared to non-users.
Conclusions
Current users of oral contraceptives had poorer periodontal health compared to non-users. Oral contraceptives may increase the risk of severe gingivitis after 12 months of use. Periodontal disease is not a contraindication for oral contraceptives, but the maintenance of a good oral hygiene should be encouraged, especially the reduction of dental plaque.

DOI: 10.1530/endoabs.37.EP215

EP216

Relationship between androgen levels and markers of endothelial dysfunction in men with type 2 diabetes

Irina Khripun, Igor Belousov, Sergey Vorobiev, Elizaveta Dzantieva, Zalina Gusova, Valentina Puzireva, Asiat Sultanmuradova & Maria Haritonova
Rostov State Medical University, Rostov-on-Don, Russia.

It is well known that type 2 diabetes causes the endothelial dysfunction. However, insufficient attention is paid to the role of androgen deficiency in the formation of the early signs of endothelial dysfunction. The aim of the work was to evaluate the relationship between testosterone deficiency and markers of endothelial dysfunction in men with type 2 diabetes.
Materials and methods
Were examined 88 men aged 40–65 years with type 2 diabetes. All patients were divided into two groups matched for age. The first group included 47 patients with normotestosteronemy, the second – 41 men with testosterone concentration below 12 nM/l. Statistical analysis was performed using analysis of the median (Me [UQ; LQ] and comparison of two independent groups (U - Mann Whitney).
Results and discussion
We didn't found statistically significant difference between the two groups in a concentration of E-selectin, P-selectin and VCAM-1. In the second group was found a significant increase of resistin ($P = 0.01$): 5.81 (5.05; 8.7) ng/ml at the interval of values (2.98–18.52) vs 4.82 (3.63; 6.34) ng/ml (0.97–13.27) and ICAM-1 ($P = 0.04$): 512.45 (350.1; 644.4) ng/ml vs 361.15 (256,8; 478.5) ng/ml. In addition, was observed an increase in CRP levels in patients with late onset

hypogonadism compared to eugonadal men (12.65 (10.9, 14.00) vs 6.62 (2.59; 8.61) mg/l) ($P=0.0001$).
Summary
Hypotestosteronemy in patients with type 2 diabetes increases the concentrations of markers of endothelial dysfunction and CRP level which leads to raise of cardiovascular risk in these patients. Research of resistin and ICAM-1 concentrations in patients with type 2 diabetes and androgen deficiency reveals endothelial dysfunction at the early stage.
Supported by: Russian Science Foundation, No. 14-25-00052.
Disclosure
Supported by: Russian Science Foundation, № 14-25-00052.
DOI: 10.1530/endoabs.37.EP216

EP217

Subclinical hypothyroidism in patients with polycystic ovary syndrome
Hamiyet Yılmaz Yasar[1], Omercan Topaloglu[1], Mustafa Demirpence[1] & Banu Ozturk Ceyhan[2]
[1]Tepecik Research and Training Hospital, Izmir, Turkey; [2]Medline Hospital, Aydin, Turkey.

Objective
Polycystic ovary syndrome (PCOS) is a common endocrine metabolic disorder that affects 5–10% of women of reproductive age. In various studies, it was found to be associated with subclinical hypothyroidism. Serum TSH levels were also reported to be increased in obese individuals. In order to define the impact of obesity on the subclinical hypothyroidism observed in patients with PCOS, we aimed to investigate subclinical hypothyroidism both in lean and overweight or obese PCOS patients.
Methods
The study included 95 lean and 122 overweight or obese women with a diagnosis of PCOS defined in accordance with the Rotterdam criteria. The control group consisted of age and BMI matched healthy individuals and grouped as lean (n: 66) and or obese (n: 65) controls. Women with chronic disease such as overt hypo- or hyperthyroidism, kidney or liver failure, hyperprolactinaemia, late-onset adrenal hyperplasia, and diabetes were excluded from the study. Anthropometric data (BMI and waist circumference) was recorded and hirsutism in accordance with Ferriman–Gallway index was evaluated. Plasma glucose and lipid profile, TSH, free T_3, free T_4, anti-thyroperoxidase antibody, anti-thyroglobulin antibody and insulin levels were measured in all study subjects. FSH, LH, total testosterone, oestradiol and DHEA-S levels were measured in patients with PCOS.
Results
There were no significant differences between all groups with respect to glucose, free T_3, free T_4, anti-thyroperoxidase antibody and anti-thyroglobulin antibody levels. Insulin and TSH levels were significantly increased in both overweight or obese women with PCOS and overweight or obese control with respect to lean groups (pinsulin: 0.001, pTSH: 0.029). But no correlation was observed between TSH levels and other studied parameters.
Conclusion
TSH elevations observed in patients with PCOS may be associated with obesity rather than the effect of PCOS.
DOI: 10.1530/endoabs.37.EP217

EP218

Subclinical hypothyroidism in young women with polycystic ovary syndrome
Yllka Themeli[1,2], Kozeta Mustafaraj[2,3], Gjergji Dilo[4] & Lindita Hoxha[4]
[1]'IKEDA' Hospital, Tirana, Albania; [2]DC'Med.al', Tirana, Albania; [3]DC'La vita', Tirana, Albania; [4]DC'Dermolife', Tirana, Albania.

Background
Separately, polycystic ovary syndrome (PCOS) and subclinical hypothyroidism (SCH) exert adverse effects on metabolic parameters. This study evaluated whether SCH in women with PCOS affects clinical, hormonal, and metabolic parameters.
Aim
To analyse the relationship between selected clinical and metabolic parameters in young women with PCOS and normal thyroid function or SCH.
Materials and methods
In this cross-sectional cohort study were enrolled 80 women diagnosed with PCOS. Their clinical, hormonal, and metabolic parameters were evaluated. SCH was defined as TSH levels of 4.5–10 mIU/l.
Results
The mean age of the 80 women was 26 ± 4.6 years. Mean BMI was 34.1 ± 6.4 kg/m^2. Thyroid function was normal in 64 women, and 16 had SCH. Prolactin and serum LDL cholesterol levels were significantly higher in the women with SCH (18.2 ± 6.2 ng/ml and 131.3 ± 17.4 mg/dl, respectively) compared with those with normal thyroid function (13.2 ± 9.7 ng/ml and 107.2 ± 29.4 mg/dl, respectively). No changes in other lipid profile parameters, insulin resistance or phenotypic manifestations were observed.
Conclusions
In young women with PCOS, SCH is associated with higher LDL cholesterol and prolactin levels. These two altered parameters should be considered as the SCH predictors in women diagnosed with PCOS.
DOI: 10.1530/endoabs.37.EP218

EP219

The relationships of bisphenol A levels with leptin and adiponectin in premenopausal women
Sevgi Polat[1], Banu Sarer Yurekli[2], Gokcen Unal Kocabas[1], Raika Durusoy[3], Murat Aksit[4], Giray Bozkaya[4], Arif Yuksel[1] & Fusun Saygili[1]
[1]Endocrinology Department, Bozyaka Education and Research Hospital, Izmir, Turkey; [2]Endocrinology Department, Faculty of Medicine, Ege University, Izmir, Turkey; [3]Public Health Department, Faculty of Medicine, Ege University, Izmir, Turkey; [4]Biochemistry Department, Bozyaka Education and Research Hospital, Izmir, Turkey.

Aim
Bisphenol A (BPA) is the most common endocrine disruptor among environmental estrogens. BPA is an ingredient that is commonly used in polycarbonate plastics. In this study, our main concern is to measure the levels of BPA in premenopausal obese women and to examine the relationship of BPA with adiponectin and leptin.
Materials and methods
47 obese women and 39 non-obese healthy women were enrolled in this study. All participants were premenopausal. In this cross-sectional study, all participant's BPA, adiponectin and leptin levels were measured. BPA levels in serum were measured by ELISA method. Obese and control group mean values were compared by t-test. BPA's relationship with other parameters were analysed by Spearman rank correlation. The average values were presented with the standard deviation.
Results
The average age of obese premenopausal women were 34.4 and 33.4 in the control group ($P=0.56$). BMI mean value of the obese participants was 34.1 ± 4.0 kg/m^2 and the control group's mean BMI value was 22.8 ± 1.6 kg/m^2 ($P<0.001$). BPA levels in obese women were significantly higher than the control group (1.19 ± 8.12 ng/ml, in obese and 9.5 ± 1.13 ng/ml in the control group, $P=0.001$). All groups in the analysis; there were a significant positive correlation between leptin and BPA levels ($r=0.317$, $P=0.003$), and a negative correlation between BPA levels and adiponectin ($r=-0.269$, $P=0.012$).
Conclusion
There are many recent studies showing the relationship between BPA and obesity. The effects of BPA that impair the regulation of body weight and lead to obesity may be related to the disruptive effects on adipocyte differentiation, fat deposition, insulin resistance and impact on the secretion of adiponectin.
DOI: 10.1530/endoabs.37.EP219

EP220

Characteristics of body composition in different phenotypes of women with polycystic ovary syndrome
Dusan Ilic[1], Djuro Macut[1], Ivana Bozic Antic[1], Jelica Bjekic Macut[2], Danijela Vojnovic Milutinovic[3], Bojana Popovic[1], Tamara Bogavac[1], Biljana Kastratovic Kotlica[4], Tatjana Isailovic[1], Valentina Elezovic[1] & Sanja Ognjanovic[1]
[1]Clinic of Endocrinology, Diabetes and Metabolic Diseases and Faculty of Medicine, University of Belgrade, Belgrade, Serbia; [2]CHC Bezanijska kosa, Belgrade, Serbia; [3]IBISS, Belgrade, Serbia; [4]Clinic of Gynecology and Obstetrics, and Faculty of Medicine, University of Belgrade, Belgrade, Serbia.

Obesity is closely associated with PCOS and worsens its metabolic and reproductive characteristics. The aim of this study was to evaluate body

composition in different PCOS phenotypes. We evaluated 365 PCOS women (PCOS: 25.05±6.24 kg/m^2; 25.48±5.21 years) diagnosed using ESHRE/ASRM criteria and 125 BMI-matched healthy women (Controls: 25.41±5.16 kg/m^2; 30.35±5.62 years). PCOS were analyzed through four phenotypes: a (anovulation (ANOV), hyperandrogenism (HA), polycystic ovary morphology (PCOM)), B (ANOV, HA), C (HA, PCOM) and D (ANOV, PCOM). In all subjects body composition was evaluated using bioelectrical impedance (Tanita). We analyzed basal metabolic rate (BMR), whole body fat mass (WBFM), whole body fat free mass (WBFFM), total body water (TBW), abdominal fat mass (AFM), abdominal fat free mass (AFFM), legs fat mass (LFM). Ratio upper body (arms+abdomen)/legs fat mass was calculated.
BMI of phenotypes were: A: 25.11±6.36, B: 27.03±6.96, C: 25.63±5.84, D: 21.41±3.93 kg/m^2. PCOS in comparison to controls had higher WBFM (24.42±13.50 vs 18.19±11.75 kg, $P<0.001$), AFM (12.17±7.68 vs 8.84±6.59 kg, $P=0.002$), LFM (4.50±2.03 vs 3.84±2.04 kg, $P=0.006$) and ratio upper body/legs fat mass (2.80±0.82 vs 2.39±0.75, $P=0.007$). There were no differences in BMR, WBFFM, TBW, AFFM between whole PCOS group and Controls. Phenotype D had lower BMI, WBFM, AFM and higher LFM than all other phenotypes ($P<0.005$). Phenotypes B and C had higher BMR, TBW and AFFM than phenotypes A and D and higher ratio upper body (arms+abdomen)/LFM than phenotype D ($P<0.005$). Phenotype B had higher WBFM and LFM than phenotype A ($P<0.005$). Our results demonstrated that body composition could relate to the androgenic status. Accordingly, phenotype B expressed the most altered body composition structure.

DOI: 10.1530/endoabs.37.EP220

EP221

Copy number variations in the X chromosome of Klinefelter syndrome

Alberto Ferlin[1], Maria Santa Rocca[1], Vanna Pecile[2], Riccardo Selice[1], Nicola Caretta[1] & Carlo Foresta[1]
[1]Department of Medicine, University of Padova, Padova, Italy; [2]Institute for Maternal and Child Health, IRCCS 'Burlo Garofalo', Trieste, Italy.

Introduction
Klinefelter syndrome (KS) is characterised by the presence of at least one extra X chromosome and represents the most common chromosomal aberration in men. Apart from infertility, the clinical spectrum of KS is variable and often not directly related to hypogonadism, whose expression is also not unpredictable. Several genetic mechanisms may explain the clinical features and variability of the phenotype in KS. In particular, gene-dosage effects and the parental origin of the supernumerary X chromosome in conjunction with (possibly skewed) X-chromosome inactivation may play significant roles. Here we investigated, for the first time, the genetic property of the X chromosomes by analysis of Copy Number Variations (CNV).
Materials and methods
We studied 93 non-mosaic (47,XXY) KS and 85 controls (46,XY men and 46,XX women) by SNP array using thel HumanOmniexpress Bead Chip 700K (Illumina), which includes more than 700 000 SNP markers. Data generated on the Illumina Infinium platform have been analysed by the GenomeStudio software v2011.1 (cnvpartition 3.1.6) and PennCNV.
Results
In KS the total number of CNV was 6.5/patient, significantly higher than 46,XY males (3.9 CNVs/patient) and 46,XX females (1.5 CNVs/patient). These CNV included duplications/patient and 12 deletions/patient, both significantly higher with respect to normal males and females. Also the total length of duplications and deletions, and the length of duplications and deletions per patient were significantly different from controls. After exclusion of CNV mapping to the PAR1 (69 CNVs) and PAR2 (six CNVs), regions of X–Y homology (401 CNVs), centromere (72 CNVs), and CNVs not containing genes (seven CNVs), we identified 94 CNVs in KS, ten in 46,XY men and 37 in 46,XX women. The number of deletion/patient and the length of deletion/patient were higher in KS with respect to controls. Furthermore, we identified 12 CNVs in genic regions that were patient-specific.
Conclusion
This is the first study showed the spectrum of CNVs in the X chromosomes in KS and might be important in better understanding the biology of the X chromosome in this syndrome and the role of CNVs in the genotype-phenotype relation.

DOI: 10.1530/endoabs.37.EP221

EP222

Circulating levels of FSH in men are genetically determined: study of the combined effect of polymorphisms in FSHR and FSHB genes

Alberto Ferlin, Cinzia Vinanzi, Elena Speltra, Manuel Pengo, Maria Santa Rocca & Carlo Foresta
Department of Medicine, University of Padova, Padova, Italy.

Introduction
Polymorphisms in the gene for FSH receptor (FSHR) and FSH β subunit (FSHB) might modulate FSH levels and represent genetic markers for a pharmacogenetic approach to male infertility treatment. rs6166 (c.2039 A>G, Asn680Ser) and rs1394205 (c.−29 G>A) in FSHR have been better analysed in women, whereas rs10835638 (−211 G>T) in FSHB seems to have a determinant role especially in men. However, studies considering the combined effect of these three polymorphisms have not been conducted.
Materials and methods
We studied 572 consecutive infertile males (including 93 with azoospermia-cryptozoospermia, 231 with oligozoospermia and 248 with normozoospermia) by means of semen analysis, FSH, LH, and T levels, testicular volume, and rs6166, rs1394205 and rs10835638 genotyping by RFLP and direct sequencing.
Results
The *FSHB* promoter polymorphism 211 G>T is significantly associated with FSH levels (9.6±7.6, 7.2±5.8 and 2.6±1.9 IU/l respectively in men GG homozygotes, GT heterozygotes and TT homozygotes, $P<0.001$). The polymorphisms −29 G>A and Asn680Ser in *FSHR* taken alone were not associated with different FSH concentrations. Combined analysis of the three polymorphisms showed again that the major determinant of FSH levels is the −211 G>T polymorphisms, only slightly modulated by the −29G>A polymorphism, so that men with the genotype −211 GG/−29 GG had the highest levels of FSH and men with the genotype −211 TT/−29 AA the lowest. Polymorphism Asn680Ser in *FSHR* had no effect neither alone nor in combined analysed. The three polymorphisms had no effect on LH and T levels, and in accordance in these data the total number of sperm and testicular volume are modulated by the genotype. TT homozygotes for the −211 SNP are invariably azoo-oligozoospermic with low testicular volume and FSH levels <8 UI/l.
Conclusions
This is the first study analysing the combined contribution of the most common polymorphisms in *FSHR* and *FSHB* genes in influencing male reproductive system and showed that −211 G>T in *FSHB* has a determinant role, in determining FSH levels, sperm count and testicular volume. This polymorphism alters the transcriptional activity of the gene, and therefore it determines a sort of isolated FSH deficiency with azoo-oligozoospermia and represents the ideal pharmacogenetic marker of FSH treatment.

DOI: 10.1530/endoabs.37.EP222

Calcium and Vitamin D metabolism

EP223

Development of an ELISA for the measurement of free 25OH vitamin D

Nicolas Heureux[1], Michel Anciaux[1], Martin Poncelet[1], Fabienne Mathieu[1], Leon Swinkels[2], Tonnie Huijs[2], Saskia Boerrigter[2], Ernst Lindhout[2], Gregg Mayer[2] & Mike Martens[2]
[1]DIAsource Immunoassays, Louvain-la-Neuve, Belgium; [2]Future Diagnostics BV, Wijchen, The Netherlands.

The objective of this project was to develop and characterise a simple immunoassay for the quantification of free 25-hydroxyvitamin D (25OH Vit D). Recent studies suggest that the concentration and genotype of vitamin D binding protein (DBP) are important factors that determine the bioavailability of 25OH Vit D in blood. It has been suggested that measurement of free, non-protein bound 25OH Vit D in serum, may provide more relevant diagnostic information than total 25OH Vit D, for instance in chronic kidney disease, bladder cancer and pancreatic cancer, or in haemodialysis patients. A two-step enzyme-linked immunosorbent assay (ELISA) was developed for the quantification of free 25OH Vit D assay, using a highly specific anti-25OH Vit D monoclonal antibody. The assay was calibrated against a symmetric dialysis method. The calibrator range was 0–35 pg/ml. The LoB was 1.1 pg/ml; the LoD was 1.7 pg/ml. Total assay precision was 5.7% at 6.3 pg/ml, 3.8% at 15.9 pg/ml and 4.8% at 24.8 pg/ml. The assay was recently compared with calculated free 25OH Vit D in clinical populations (J Schwartz J. Clin. Endocrinol. Metab. 2014). An assay was developed that reproducibly determines the level of free 25OH Vit D in serum. The assay

can be used as a valuable tool in studies to establish the clinical relevance of free 25OH Vit D.

DOI: 10.1530/endoabs.37.EP223

EP224

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

Faiza Qari
King Abdulaziz, Jeddah, Saudi Arabia.

A 55-year-old Saudi woman with a complaint of anterior maxilla mass of 1 month duration. Initial examination revealed a painful mass in the anterior maxilla. Surgery was not undertaken because routine laboratory investigations revealed hypercalcemia.
Initial laboratory tests performed on admission showed the following: alkaline phosphates 143 IU/l, corrected serum calcium 3.2 mmol/l, PTH 120 pmol/l A provisional diagnosis was made for hypercalcemia due to hyperparathyroidism. Technetium thallium (99mTc-201Th) subtraction scintigraphy (Sestamibi scanning), which demonstrated a single, ectopic anterior mediastinal parathyroid adenoma. Treatment was initiated by hydration and intravenous bisphosphonate. Initially the patient underwent extirpation of the mass and curettage of the bone. Histological sections showed multiple giant cells consistent with Brown tumour of primary hyperparathyroidism. She underwent mediastinal parathyroidectomy by median sternotomy. The post-operative course was uneventful and the patient was discharged on the 6th post-operative day without complications. postoperative laboratory tests were normal.
Conclusions
Due to recent improvements in analytical techniques, the diagnosis of hyperparathyroidism usually occurs when the disease is in an asymptomatic phase, and the incidence of patients with advanced bone lesions is rare. The treatment of choice for bone lesions is parathyroidectomy.

DOI: 10.1530/endoabs.37.EP224

EP225

Influence of vitamin D binding protein and C3-epimer on accuracy of 25OH vitamin D ELISA assays

Nicolas Heureux, Michel Hars & Fabienne Mathieu
DIAsource Immunoassays, Louvain-la-Neuve, Belgium.

The measurement of 25OH vitamin D has tremendously evolved since the first competitive protein-binding assay. Amongst the different techniques that are now routinely employed, ELISA still represents a common tool to quantify the level of 25OH Vitamin D in individuals. Several 25OH Vitamin D ELISA assays have been developed and commercialized in the last 3 years. They all differ by the antibody used and by the technology that is applied to release 25OH Vitamin D from its binding proteins. While chemiluminescence based assays (CLIA) have been extensively evaluated and compared in the literature, virtually no studies have been conducted on the 25OH Vitamin D ELISA assays. Six commercially available 25OH Vitamin D ELISA have been compared towards increasing concentration of Vitamin D binding protein (DBP) and C3-epi-25OH Vitamin D3 (C3-epimer). The concentration of DBP in human blood is not constant and can be influenced by a number of factors including obesity, pregnancy, the use of oral contraceptives, hormone replacement therapy, liver disease, renal disease, proteinuria and intensive care. On the other hand, C3-epimer is present in the circulation of the majority of adults and children, with levels up to 93 ng/ml reported. The DIAsource Immunoassays ELISA was the only assay not being negatively biased by the addition of increasing amounts of DBP. Mean bias of -6 to -21% were observed with the other assays. Two assays were clearly impacted by the addition of C3-epimer, with mean positive bias of 28 and 30%. The performance of a 25OH Vitamin D immunoassay is mainly influenced by the choice of the antibody and by the efficiency of the method that is used to release 25OH Vitamin D from its binding proteins. Half of the assays involved in this study were significantly impacted by the addition of endogenous interferents. This confirms that 25OH Vitamin D remains a difficult assay.

DOI: 10.1530/endoabs.37.EP225

EP226

Pitfalls in the interpretation of bone turnover markers in liver transplantation

Charlotte Krol[1], Desi Meiland[1], Olaf Dekkers[1], Eveline van der Veer[2], Herman Kroon[1], Ton Rabelink[1], Bart van Hoek[1] & Neveen Hamdy[1]
[1]Leiden University Medical Centre, Leiden, The Netherlands; [2]Groningen University Medical Centre, Groningen, The Netherlands.

Introduction
Osteoporosis and fractures are common in liver disease and fracture incidence increases after orthotopic liver transplantation (OLT). The value of bone turnover markers (BMTs) in the prediction of bone loss and fracture risk pre- and post-OLT is not known.
Study design
The BMTs P1NP, osteocalcin, BALP and CTX were measured initially or in Biobank stored sera at screening and at 3, 6 and 12 months post-OLT in consecutive OLT recipients between 2008 and 2011. A prerequisite was the availability of BMD data and of spinal radiographs at screening and 6 and 12 months post-OLT.
Results
51 patients (80% male, median age 59 years) were included. Most common liver pathology was alcoholic (41%) and viral liver disease (26%). At screening, osteoporosis and osteopenia were prevalent in respectively 16 and 33% at the lumbar spine (LS) and 4 and 44% at the femoral neck (FN), and vertebral fractures were prevalent in 67%. Post-OLT, LS BMD remained stable but FN BMD decreased and 43% of patients developed new fractures. At screening, P1NP and CTX levels were high and osteocalcin levels low, but only CTX levels were predictive for bone loss and fracture risk. An increase in BALP at 6 month post-OLT was predictive for fracture risk a year post-OLT.
Conclusion
Despite the many pitfalls in the interpretation of particularly collagen-derived BTMs in liver disease, high CTX levels pre- OLT and an increase in BALP post-OLT were respectively predictive for bone loss and fracture risk during the first post-OLT year.

DOI: 10.1530/endoabs.37.EP226

EP227

The evaluation of oxidative status via the measurements of total oxidant status, total anti-oxidant status, ischaemia-modified albumin and oxidised-low density lipoprotein in patients with vitamin D deficiency

Husniye Baser[1], Ummugulsum Can[2], Salih Baser[3], Bahauddin Taha Hidayetoglu[3], Uysaler Aslan[3], Ilker Buyuktorun[3] & Fatma Humeyra Yerlikaya[4]
[1]Department of Endocrinology and Metabolism, Konya Education and Research Hospital, Konya, Turkey; [2]Department of Biochemistry, Konya Education and Research Hospital, Konya, Turkey; [3]Department of Internal Medicine, Konya Education and Research Hospital, Konya, Turkey; [4]Department of Biochemistry, Necmettin Erbakan University Faculty of Medicine, Konya, Turkey.

Introduction
Oxidative damage may be responsible for pathogenesis and complications of many diseases. Vitamin D deficiency has been suggested as a potential mediator of various extra-skeletal pathologies. However, there are limited data on anti-oxidant properties of vitamin D.
Methods
Forty-one subjects with vitamin D deficiency and 30 healthy controls were enrolled in the study. The levels of total anti-oxidant status (TAS), total oxidant status (TOS), ischaemia-modified albumin (IMA), oxidized-low density lipoprotein (ox-LDL), high-sensitivity C-reactive protein (hs-CRP) and fibrinogen were measured in the patient and control groups. These measurements were repeated in 17 patients after the replacement of vitamin D.
Results
Serum IMA and TOS levels were significantly higher ($P<0.001$ and $P=0.035$, respectively), while TAS levels were significantly lower in patients, compared with controls ($P<0.001$). Additionally, fibrinogen was significantly higher in patients than controls ($P=0.003$), while ox-LDL and hs-CRP levels were similar between two groups. After the replacement of vitamin D, TAS level was significantly increased ($P=0.037$), and TOS and fibrinogen levels were significantly decreased ($P=0.043$ and $P=0.010$, respectively). Vitamin D levels were negatively correlated with IMA and fibrinogen levels ($r=-0.500$, $P<0.001$ and $r=-0.391$, $P=0.002$, respectively), although positively

correlated with TAS levels ($r=0.430$, $P<0.001$). No correlation was found between vitamin D levels, and TOS, ox-LDL and hs-CRP levels.
Conclusions
In this study, while serum IMA, TOS and fibrinogen levels were increased, TAS levels were seen to be decreased in patients with vitamin D deficiency. These results suggest that oxidative/anti-oxidative balance shifts in favours of oxidative status in vitamin D deficiency.

DOI: 10.1530/endoabs.37.EP227

EP228

Vitamin D status among the doctors in a tertiary referral centre in Kerala

Mavila Veetil Vimal, P Abdul Majeed & M C Naseerali
Malabar Institute of Medical Sciences, Calicut, Kerala, India.

Vitamin D deficiency is very common in India. Doctors are vulnerable to Vitamin D deficiency since they are almost always indoors. The purpose of this study was to assess the Vitamin D status among doctors in a tertiary referral centre in Kerala, a southern state of India.
Methods
Levels of Vitamin D, calcium, phosphorus, alkaline phosphatase, and parathyroid hormone were assessed among 82 doctors and 50 healthy control subjects using ChemiLuminescence immunoassay.
Results
Vitamin D deficiency (<20 ng/ml) was seen among 93.9% of the study group compared to 40% of the control group. Severe Vitamin D deficiency was seen among 54.9% of the study group and only 3.3% of control group. There was no significant correlation between the levels of vitamin D and other biochemical parameters – calcium, phosphorus,and alkaline phosphatase but there was significant negative correlation with Parathyroid hormone levels.
Conclusion
Vitamin D deficiency is highly prevalent among doctors in Southern part of India.

DOI: 10.1530/endoabs.37.EP228

EP229

The relationship between vitamin D and non-alcoholic fatty liver disease in type 2 diabetic Egyptian patients

Randa Fayez Abd-el-Salam[1], Moustafa Mamdouh Sayed[2], Sahar Al-Wakeel[1], Inas Kostandi Malaty[1] & Laila Rashed[1]
[1]Faculty of Medicine – Cairo University, Cairo, Egypt;
[2]Al-Nakheel Hospital, Cairo, Egypt.

Background
Diabetes mellitus, hypovitaminosis D, and non-alcoholic fatty liver disease (NAFLD) are common medical conditions that share some risk factors, one of which is obesity. Both NAFLD and vitamin D deficiency have been linked to the development of metabolic syndrome and type 2 diabetes. The aim of this study is to evaluate the level of serum 25-hydroxy vitamin D [25(OH)D] in type 2 obese diabetic Egyptian patients with variable degrees of hepatic steatosis.
Methods
Sixty type 2 obese diabetic patients were recruited. BMI, HbA1c, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ glutamyl transpeptidase (GGT), lipid profile, and 25(OH)D were measured. NAFLD was assessed semi-quantitatively by ultrasound on a scale of 0–3.
Results
There was a significant negative correlation between 25(OH)D and age, $P=0.027$; HbA1c, $P=0.000$; triglycerides (TG), $P=0.022$ and degree of steatosis, $P=0.047$. 25(OH)D showed a significant positive correlation with HDL, $P=0.046$. ANOVA showed a significant association between the degree of steatosis and BMI, $P=0.000$. Using multivariate analysis HbA1c was the only significant predictor for vitamin D level when tested with BMI and duration of diabetes, $P=0.000$. Patients were divided into two subgroups according to 25(OH) D level; group 1 had normal levels, group 2 were deficient in 25(OH)D. There was a significant difference between both groups as regards age, $P=0.035$; HbA1c, $P=0.000$; TG, $P=0.004$; and HDL, $P=0.028$, with vitamin D deficient patients showing higher age, higher HbA1c, higher TG and lower HDL levels. The two groups did not differ significantly as regards the grading of hepatic steatosis.
Conclusion
Poor glycaemic control is associated with lower levels of 25(OH)D independent of BMI. Higher degrees of steatosis correlated with hypovitaminosis D.

DOI: 10.1530/endoabs.37.EP229

EP230

Study of vitamin D levels in adult males in Dakahlia Governorate

Raef Botros, Rania Sayed, Merhan Nasr & Mohamed Yassin
Ain Shams University, Cairo, Egypt.

Background
Vitamin D is a growing endemic problem. Wide proportions of healthy adults are deficient in vitamin D. It is very important for skeletal and non-skeletal health. It is now well established that many people have vitamin D levels that are less than currently recommended for optimal health
Aim of this work
To assess vitamin-D sufficiency/deficiency in a sample of healthy Egyptian adult males in Dakahlia Governorate in Northern Egypt and correlate it to social status, Sun exposure and Vitamin D intake in food.
Subjects and methods
This cross-sectional study was conducted on 90 healthy Males selected randomly from the relatives of patients in Outpatient Clinics and Internal Medicine Departement of El-Gamalia General Hospital. Medical History, Dietary Questionnaire and Sun exposure Questionnaire were taken from all participants who were clinically examined as well. Laboratory investigations including hemoglobin, serum creatinine, ionized calcium were measured in all subjects and 25-(OH) vitamin D was measured in 57 subjects.
Results
Forty four out of 57 subjects (77%) had deficient vitamin D levels (<20 ng/ml), eight (14%) had insufficient levels (21–30 ng/ml) and five (9%) had sufficient levels (>30 ng/ml). 55.6% of our subjects had moderate intake of vitamin D rich foods while 18.9% had high intake and 25.6% had low intake. Fifty three subjects had indoor occupations while 37 subjects had outdoor occupation. Sun exposure was found to be positively and significantly correlated with vitamin D levels, ($R=0.37$, P value 0.005). Vitamin D was positively and significantly correlated to sun exposure in case of moderate intake of vitamin D rich foods only, (R 0.419, P value 0.021) and for indoor activities, (R 0.451, P value 0.005). Multiple regression analysis showed that intake of vitamin D rich foods was an independent predictor for vitamin D level.
Conclusion
Our results show a high rate of hypo-vitaminosis D in adult Egyptian Males in Dakahlia Governorate.

DOI: 10.1530/endoabs.37.EP230

EP231

Is there a relationship between neutrophil/lymphocyte ratio and vitamin D levels in individuals over 65 years of age?

Merve Yilmaz[1], Arzu Gedik[2], Tevfik Demir[3], Ayten Eraydin[4], Dilek Cimrin[5], Abdurrahman Cömlekci[3] & Sevinc Eraslan[3]
[1]Endocrinology Department, Samsun Gazi State Hospital, Samsun, Turkey; [2]Endocrinology Department, Agri State Hospital, Agri, Turkey; [3]Endocrinology Department, Dokuz Eylül University Medical Faculty, Izmir, Turkey; [4]Endocrinology Department, Gaziantep University Medical Faculty, Gaziantep, Turkey; [5]Biochemistry Department, Dokuz Eylul University Medical Faculty, Izmir, Turkey.

Introduction
Vitamin D deficiency may be an important predisposing factor for infections as well as autoimmune diseases in old individuals. Neutrophil/lymphocyte ratio (NLR), is a meaningful indicator of inflammation throughout the body. In this study we aimed to show, whether or not a relationship exists between vitamin D levels and NLR in patients older than 65 years.
Materials and method
Data of 82 patients over 65 years of age was retrospectively examined. Those without chronic renal or liver failure, active infection or disease affecting hemogram values and bone metabolism were included to study. Complete blood count and vitamin D levels of patients were recorded. NLR was calculated.

The correlation analysis was done on patients, in order to understand whether the relationship between vitamin D levels and NLR exists.
Results
The mean level of vitamin D was 21.20±10.99 and NLR was 2.09±0.97. Patients were divided into four groups according to the level of vitamin D. There was not statistically significant difference between the groups in terms of NLR ($P=0.433$). When the patients were divided into two groups according to the adequate (>30 ng/ml) and inadequate (≤30 ng/ml) levels of vitamin D, there was not significant difference between the groups in terms of NLR ($P=0.169$). Significant correlation was not detected between the mean vitamin D levels and NLR in patients. There was not significant correlation between vitamin D levels and NLR, even when divided into three groups according to their age.
Conclusions
An important relationship between vitamin D levels and immune system function has been reported. Increase in NLR, which is an indicator of acute phase response, is associated with poor prognosis in various diseases. In our study, there was not significant relationship between vitamin D levels and NLR. However, there is not any study done on this topic in the literature. Further studies with higher number of patients may be beneficial.

DOI: 10.1530/endoabs.37.EP231

EP232

Relationship among plasminogen activator inhibitor-1, bone mineral density, metabolic and bone turnover markers in postmenopausal women with type 2 diabetes mellitus

Silvija Canecki-Varzic[1,2], Ines Bilic-Curcic[1,2] & Ivana Prpic-Krizevac[1,2]
[1]Clinical Hospital Center Osijek, Osijek, Croatia; [2]Faculty of Medicine, University of Josip Juraj Strossmayer, Osijek, Croatia.

Background
Women with type 2 diabetes mellitus (T2DM) have a higher risk of fractures despite increased bone mineral density (BMD). In experimental studies a potential role of plasminogen activator inhibitor-1 (PAI-1) in bone remodelling is suggested but studies in humans are lacking. This is a first study in humans investigating whether circulated levels of PAI-1 in postmenopausal women with T2DM are related to BMD and adiposity.
Methods
Anthropometric variables, PAI-1 and insulin levels, serum lipids and bone turnover markers were measured in 117 postmenopausal women with T2DM. A total of 117 female patients were divided according to lumbar spine BMD measurements via dual-energy X-ray absorptiometry in three groups: 47 with osteopenia, 21 with osteoporosis and 49 with normal BMD.
Results
Diabetic patients with normal BMD had significantly higher BMI, greater waist circumference and lower bone turnover markers than diabetics with osteopenia and osteoporosis ($P<0.01$). PAI-1 was lower in diabetics with osteoporosis and osteopenia compared with diabetics with normal BMD ($P<0.05$). In the multiple regression models the strongest determinants of PAI-1 among metabolic parameters were triglyceride and insulin levels and the duration of T2DM, among therapy beta blockers, and among bone markers pyrilinks ($P<0.05$). Final regression analysis model revealed insulin ($P=0.003$), triglycerides levels ($P=0.0002$) and pyrilinks ($P=0.0002$) to be the strongest predictors of PAI-1 levels in all patients.
Conclusion
Our findings suggest that the PAI-1 has a protective effect on bone loss by suppression of bone turnover in obese diabetic patients, and the effect is primarily mediated through the influence of metabolic factors, hyperinsulinaemia, hypertriglyceridaemia and obesity. However, the fact that pyrilinks is also independently correlated to PAI-1 implies its direct involvement in bone metabolism influencing bone mass and strength.

DOI: 10.1530/endoabs.37.EP232

EP233

Different influences of physiological and medicamentous hyperprolactinaemia on calcium metabolism in rats – experimental study

Danijela Radojkovic[1,2], Milica Pesic[1,2], Sasa Radenkovic[1,2], Slobodan Antic[1,2], Marija Vukelic Nikolic[1] & Tatjana Jevtovic Stoimenov[1]
[1]Medical Faculty, University Nis, Nis, Serbia; [2]Clinic of Endocrinology, Diabetes and Metabolic Disorders, Clinical Center Nis, Nis, Serbia.

Introduction
The aim of this study was to compare prolactin receptor gene (*Prlr*) expression in the duodenum, vertebra and kidney, during physiological and medicamentous hyperprolactinaemia.
Methods
Wistar female rats 18 weeks old were divided into: Group P: nine rats, 3 week pregnant; Group M: ten rats that were intramuscular administrated Sulpirid (10 mg/kg) twice daily for 3 weeks; and age matched nulliparous rats as a control group: ten rats, 18 weeks old (C). Laboratory analysis included: prolactin, serum ionized calcium, phosphorus, urinary calcium and phosphorous excretion, and serum procollagen type 1 N-terminal propeptide (P1NP). Relative quantification of *Prlr* gene expression in duodenum, vertebra and kidney was determined by quantitative real time polymerase chain reaction.
Results
PRL concentrations were significantly higher in group P and M, compared to C ($P<0.001$). In the pregnancy ionized calcium was significantly decreased compared to C and M ($P<0.001$); serum phosphorus was significantly increased compared to C ($P<0.05$); urinary calcium was increased compared to C ($P<0.01$) and lower compared to M (with no significance); urinary phosphorous was significantly increased compared to C and M ($P<0.001$) and P1NP was significantly increased compared to C and M ($P<0.001$). In the physiological hyperprolactinaemia expression of *Prlr* gene was significantly higher in the duodenum ($P<0.001$) and significantly lower in the vertebra ($P<0.01$). While down-regulation of *Prlr* gene was verified in the kidney, in both groups.
Conclusions
In medicamentous hyperprolactinaemia, down-regulation of *Prlr* gene expression in duodenum could be underlying reason for diminished intestinal calcium absorption. Increased calcium uresis could be partly due to down-regulated *Prlr* gene expression in the kidney. In order to maintain calcium homeostasis, since intestinal absorption is compromised and loosing via kidney elevated, prolactin will rapidly take calcium from skeletal system, thank to increased *Prlr* gene expression in the vertebra, leading to more harmful effect on bone metabolism compering to physiological hyperprolactinaemia.

DOI: 10.1530/endoabs.37.EP233

EP234

The effects of maternal iron status on infant fibroblast growth factor-23 and mineral metabolism

Vickie S Braithwaite[1], Ann Prentice[1,2], Momodou K Darboe[2], Andrew M Prentice[2,3] & Sophie E Moore[1,2]
[1]MRC Human Nutrition Research, Cambridge, UK; [2]MRC Keneba, MRC Unit, Banjul, Gambia; [3]MRC International Nutrition Group, London, UK.

Fibroblast growth factor-23 (FGF23), a phosphate-regulating hormone is elevated in hypophosphataemic syndromes and is a predictor of mortality in patients with kidney disease. Recent findings demonstrate iron deficiency as a potential mediator of FGF23 expression and murine studies have shown *in utero* effects of maternal iron deficiency on FGF23 and phosphate (P) metabolism and bone formation (Clinkenbeard, *JBMR*, 2013).
The aim of the current study was to investigate the impact of maternal iron status on infant mineral metabolites in humans over the first two years of life. Infants born to mothers with normal (NI $n=25$) and low (LI $n=25$) iron status during pregnancy, from a mother-infant trial ISRCTN49285450 from rural Gambia, West Africa, had blood and plasma samples analysed at 12, 24, 52, 78 and 104 weeks of life for circulating haemoglobin (Hb), C-terminal (C-FGF23; Immutopics, USA) and intact-FGF23 (I-FGF23; Kainos, Japan), P, total alkaline phosphatase (TALP) and cystatin C (Cys C) (Kone Analyser 20i, Finland). Circulating I-FGF23, P, TALP and Hb decreased and estimated glomerular filtration rate (eGFR; 74.835/(cys C (mg/l)$^{1.333}$) increased over time (mean (S.D.) I-FGF23: 49.1 (13.1) to 34.3 (10.9) pg/ml, P: 1.86 (0.13) to 1.69 (0.17) mmol/l, TALP: 406 (133) to 318 (135) U/l, Hb: 10.7 (1.6) to 9.4 (1.6) g/dl and eGFR: 59.9 (11.2) to 94.5 (23.4) ml/min all $P\leq0.0001$)). C-FGF23 did not change significantly over time (402 (218) to 487 (502) RU/ml, $P=0.15$). C-FGF23 and TALP were significantly higher in LI compared with NI from 52 weeks for C-FGF23 (52 weeks: 732 (702) vs 334 (225), 78 weeks: 702 (827) vs 417 (754) and 104 weeks: 628 (628) vs 347 (283) RU/ml) and from 24 weeks for TALP (24 weeks: 373 (153) vs 306 (77), 78 weeks: 310 (106) vs 258 (66), 104 weeks: 340 (162) vs 289 (93) U/l). Adjusted for timepoint Hb was the strongest negative predictor of C-FGF23 concentration (Beta coefficient (S.E.) −104.1 (27.28) RU/ml, $P\leq0.0002$; group difference $P=0.03$) and P the strongest positive predictor of I-FGF23 (31.4 (3.9) pg/ml, $P\leq0.0001$, group difference $P=0.8$) and I-FGF23 did not predict C-FGF23 (−2.68 (3.56) RU/ml, $P=0.45$, group difference $P=0.03$). In conclusion, this study suggests that poor maternal iron

status leads to an increased infant C-FGF23 and TALP concentration in humans. Further studies are required to investigate the role of maternal iron status in the regulation of offspring FGF23 status and mineral metabolism.

Disclosure
This research was jointly funded by the UK Medical Research Council (MRC) & the Department for International Development (DFID) under the MRC/DFID Concordat agreement. MRC programmes: U105960371, U123261351 & MC-A760-5QX00.

DOI: 10.1530/endoabs.37.EP234

EP235

Vitamin D and seasonal variation among Greek female patients with osteoporosis

Georgios Papadakis, Ioannis Keramidas, Kassiani Kakava, Theodora Pappa, Vassiliki Villiotou, Paraskevi Manitarou, Styliani Kalaitzidou, Eleni Triantafillou, Victoria Kaltzidou & Anastasios Pappas
Metaxa Cancer Hospital, Piraeus, Athens, Greece

Background
25 hydroxy vitamin D (25(OH)D) vitamin levels are positively associated with bone mineral density and season, time of day and sun exposure duration influence its synthesis. Variations in daylight throughout the year and zenith angle, depending on the latitude of residence, influence u.v. solar radiation which is closely related to serum 25(OH)D levels. The aim of this study was to investigate the degree of seasonal variation of 25(OH)D serum levels in a population-based cohort of postmenopausal women with osteoporosis.
Methods
Serum levels of 25(OH)D were assessed in 596 Greek patients (mean age 65.3 years old; S.D. = 9.4) in different months between August 2012 and December 2014. Each patient contributed one blood sample during the observation period and all women received vitamin D supplements as a multivitamin tablet or as a Calcium carbonate with vitamin D chewable tablet. Total hip bone mineral density was measured by dual-energy X-ray absorptiometry and all women had a *T* score of -2.5 or less.
Results
The minimum 25(OH)D serum level was observed in March (13.4 ± 9.5 ng/ml) and the maximum levels in August, September and October (29.1 ± 16.1; 28.9 ± 12 and 28.4 ± 8.9 ng/ml respectively). The prevalence of vitamin deficiency (<20 ng/ml), insufficiency (20–<30 ng/ml) and sufficiency (≥ 30 ng/ml) in March was 76.5, 15.7 and 7.8% respectively. On the contrary, the highest prevalence of vitamin D sufficiency was observed in August, September and October (38.1, 45.3 and 46.5% respectively).
Conclusion
Seasonal variations should be considered when measuring and correcting vitamin D serum levels. Although Greece is a country with sunshine, the majority of postmenopausal women with osteoporosis do not reach sufficient 25(OH)D levels, regardless of type and dose of vitamin D supplementation and degree of sun exposure.

DOI: 10.1530/endoabs.37.EP235

EP236

Is vitamin D receptor gene polymorphism TaqI effect the occurrence and subtype of Hashimoto's thyroiditis?

Fulya Akin[1], Bedia Guleryuz[2], Sebehat Turgut[3], Senay Topsakal[1], Guzin Fidan Yaylali[1], Melek Tunc Ata[3] & Mukaddes Mergen Dalyanoglu[3]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Pamukkale University, Denizli, Turkey; [2]Department of Internal Medicine, Faculty of Medicine, Pamukkale University, Denizli, Turkey; [3]Department of Physiology, Faculty of Medicine, Pamukkale University, Denizli, Turkey.

Background
Hashimoto's thyroiditis (HT) is a common autoimmune disease of thyroiditis. There is a relation with Vitamin D levels, vitamin D receptor (VDR) and HT reported. More than 30 gene polymorphisms are found in VDR gene. The most common four types of polymorphisms studied in autoimmune disease are FokI (exon 2), BsmI (intron 8), ApaI (intron 8) and TaqI (exon 9). The aim of this study is to investigate the association between VDR TaqI gene polymorphism and HT subtypes.
Methods
We performed a case-control study that included 139 cases with HT (50 euthyroid, 50 subclinical hypothyroid, 39 overt hypothyroid patients) and 50 healthy control. Subjects were collected from Endocrinology Clinic. VDR gene polymorphisms TaqI were typed by RFLP.
Results
At the TaqI genotype distribution, 34% TT genotype, 38% Tt genotype and 28% tt genotype were identified in the control group. TT genotype in 46.9%, Tt genotype in 32.7% and tt genotype in 20.4% were identified in the euthyroid group. TT genotype in 55.1%, Tt genotype in 38.8% and tt genotype in 6.1% were detected in subclinical hypothyroid group. In evident hypothyroid group TT genotype in 31.6%, Tt genotype in 55.3% and tt genotype in 13.2% identified. In euthyroid group and subclinical hypothyroidism group TT genotype, in the evident hypothyroidism groups and the control group Tt genotype was detected at the highest rate.
Conclusion
Statistically significant differences was observed when all HT group compared with the control group according to TaqI genotype distribution. There is relationship between VDR TaqI gene polymorphism and HT. This study showed that VDR TaqI gene polymorphism may be predisposed to the HT occurrence.

Disclosure
Grant numbers 2012 TPF6.

DOI: 10.1530/endoabs.37.EP236

EP237

Relation of vitamin D receptor gene polymorphism *FOK*-I in subtype of Hashimoto's thyroiditis

Senay Topsakal[1], Bedia Guleryuz[2], Melek Tunc Ata[3], Fulya Akin[1], Guzin Fidan Yaylali[1], Mukaddes Mergen Dalyanoglu[2] & Sebahat Turgut[3]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Pamukkale University, Denizli, Turkey; [2]Department of Internal Medicine, Faculty of Medicine, Pamukkale University, Denizli, Turkey; [3]Department of Physiology, Faculty of Medicine, Pamukkale University, Denizli, Turkey.

Background
Hashimoto's thyroiditis is the most common autoimmune endocrine disorders and often leads to hypothyroidism. There is a relation with Vitamin D levels, vitamin D receptor (VDR) and HT reported. More than 30 gene polymorphisms are found in VDR gene. The most common four types of polymorphisms studied in autoimmune disease are FokI (exon 2), BsmI (intron 8), ApaI (intron 8) and TaqI (exon 9). The aim of this study is to investigate the association between VDR FokI gene polymorphism and Hashimoto's thyroiditis subtypes.
Methods
We performed a case-control study that included 139 cases with HT (50 euthyroid, 50 subclinical hypothyroid, 39 overt hypothyroid patients) and 50 healthy control. Subjects were collected from Endocrinology Clinic. VDR gene polymorphisms FokI were typed by RFLP.
Results
At the FokI genotype distribution analysis, 49% of FF genotype, 36.7% of Ff genotype and 14.3% of ff genotype were detected in euthyroid Hashimoto's thyroiditis group. The FF genotype in 46.9%, Ff genotype in 38.8% and ff genotype in 14.3% of group were detected in subclinical hypothyroidism group. In evident hypothyroidism, the FF genotype was observed in 36.8%, Ff genotype in 52.6% and ff genotype in 10.5% of the patient. In the control group, FF genotype in 58%, Ff genotype in 32% and FF genotype in 10% of the group were determined. At the FokI genotype distribution in euthyroid, subclinical hypothyroid and control groups the FF genotype was observed in the highest rate while Ff genotype was detected at the highest rate in evident hypothyroidism group. There were no statistically significant differences were observed in all Hashimoto's thyroiditis group compared with the control group. No statistically significant difference was seen between euthyroid, subclinical hypothyroid, evident hypothyroid groups and the control group.
Conclusion
This study showed that VDR FokI gene polymorphism not affected the occurrence of the HT.

Disclosure
Grant numbers 2012 TPF6

DOI: 10.1530/endoabs.37.EP237

EP238

Effect of supplementation with vitamin D and calcium to excessive suppression of bone metabolism during antiresorptive therapy

Tijana Icin[1], Branka Kovacev-Zavisic[1], Jovanka Novakovic-Paro[1], Ivana Bajkin[1], Bojan Vukovic[2], Ivanka Percic[2], Nemanja Kovacev[3] & Milica Medic-Stojanoska[1]
[1]Clinic of Endocrinology, Diabetes and Metabolic Diseases, Medical Faculty, Clinical Center of Vojvodina, University of Novi Sad, Novi Sad, Serbia; [2]Medical Faculty, Emergency Center, Clinical Center of Vojvodina, University of Novi Sad, Novi Sad, Serbia; [3]Clinic of Orthopaedic Surgery and Traumatology, Clinical Center of Vojvodina, Novi Sad, Serbia.

Introduction
Long-term therapy with bisphosphonates is considered a risk factor for the development of atypical fractures of the femur. One of the mechanisms of these fractures is excessive suppression of bone metabolism. The supplementation dose of vitamin D and calcium could have an impact on the degree of suppression of bone turnover.
The aim
To determine whether the presence or dose of supplementation with vitamin D and calcium during antiresorptive therapy have an impact on the achieved degree of suppression of bone metabolism.
Methods and materials
This was a prospective longitudinal study that included 200 postmenopausal women with antiresorptive treatment of osteoporosis. We analysed osteocalcin, CTx and ionic calcium, before treatment and 3 months after starting the therapy, and dose of supplementation with vitamin D and calcium. Based on the values of osteocalcin and CTx after 3 months of therapy, patients were divided into four groups: Group1-accelerated bone metabolism, Group2-awaited response to therapy, Group3-excessive suppression of bone resorption, Group4-excessive suppression of bone remodelling.
Results
Calcium supplementation was carried out in 77.5% of patients, usually in a dose of 500 mg/day and vitamin D in 92.5% usually at a dose of 400 IU. The dose of calcium is satisfied recommended dose in 14% of cases, a dose of vitamin D in 42.5% of cases. Calcium supplementation was not associated with the degree of suppression of bone metabolism ($P=0.557$, $\chi=0.155$). Supplementation with vitamin D was not associated with the degree of suppression of bone metabolism ($P=0.652$, $\chi=0.241$). The values of ionic calcium before and during treatment were in the reference range.
Conclusion
Most patients with antiresorptive therapy for osteoporosis takes supplementation with vitamin D and calcium. The supplementation dose in many cases was less than the recommended dose. The degree of suppression of bone metabolism during antiresorptive therapy did not depend on the supplementation dose of calcium nor vitamin D.

DOI: 10.1530/endoabs.37.EP238

EP239

Familial hypercalcaemic hypocalciuria in a woman with Graves' disease: a case report of mistaken identity

Roxana Novac
Emergency Hospital, Moinesti, Romania.

We present the case of a 58 years old woman with a long history of Graves' disease and mild hypercalcaemia (total calcium registered a maximum of 11.1 mg/dl) that was first interpreted as a consequence of hyperthyroidia. After 10 year of being treated with anti-thyroid drugs the patient finally decides to undergo surgery. Immediately after surgery this particular patient does not develop hypoparathyroidism, her calcium level remaining a little high. Six weeks after surgery under appropriate thyroid supplementation the calcium levels still remains a little high (10.8 mg/dl). The labs also show normal phosphate, with normal alkaline phosphatase, normal PTH, normal renal function. Other causes of hypercalcaemia were also excluded. We raised the suspicion of a FHH although the patient did not have any familial history. We found hypercalciuria (3 mg/24 h) and a low calcium/creatinine clearance (0.002) witch sustain our supposition. After that we started searching the same disease in the family but unfortunately we were only able to find it in her only son, her parents being already dead and she does not any other siblings. What also intrigued us in this patient is the bone density witch is not normally affected in FHH but here we found a poor mineral density (especially on radius of Ts $=-3.4$) which we interpreted as being due to the long evolution of hyperthyroidism. In conclusion we describe the case of FHH in a woman with Graves' disease in which hypercalcaemia was initially attributed to hyperthyroidism.

DOI: 10.1530/endoabs.37.EP239

EP240

Recalcitrant hypocalcaemia in a patient with post-thyroidectomy hypoparathyroidism and roux-en-y gastric bypass

Gonzalo Allo Miguel, Elena García Fernández, Soledad Librizzi, Guillermo Martínez Díaz-Guerra & Federico Hawkins Carranza
Endocrinology Service, 12 de Octubre University Hospital, Madrid, Spain.

Introduction
Roux-en-Y gastric bypass (RYGB) places patients at an increased risk of hypocalcemia due to the reduction in calcium absorption (because the procedure bypasses the duodenum and jejunum) and vitamin D deficiency. Subsequent thyroid surgery increases the risk of severe hypocalcemia due to potential post-operative hypoparathyroidism. Only a few cases have been published before of this kind of treatment-challenging hypocalcaemia.
Case report
We report the case of a 31-year-old woman with a previous RYGB, who suffered severe and symptomatic chronic hypocalcaemia after total thyroidectomy. Six months after the surgery, corrected calcium level had severely decreased (5.2 mg/dl) and the patient related generalised muscle cramps, labile mood and increased anxiety. She required aggressive therapy with oral calcium and calcitriol (highest dose: 12 g of calcium carbonate and 8 µg of calcitriol per day) and frequent calcium infusions, but there was no improvement in serum calcium level. Due to the lack of response to standard therapy, teriparatide treatment was started (first with s.c. injections and thereafter with a multipulse s.c. infusor) but the results were disappointing. As there was no response to different medical treatments, reversal of RYGB was performed with no complications and a subsequent sustained increase in serum calcium level.
Conclusions
This case shows that patients with postoperative hypoparathyroidism and RYGB have increased risk of severe recalcitrant symptomatic hypocalcaemia. In our case teriparatide was ineffective but, as this is the first patient reported, more results are needed to evaluate properly the effect of teriparatide in this kind of hypocalcaemia. The reversal of RYGB may be an optimal treatment, if medical management has failed, because the surgery recovers an adequate absorption of calcium and vitamin D from previously bypassed duodenum and proximal jejunum.

DOI: 10.1530/endoabs.37.EP240

EP241

Hypovitaminosis D in pregnancy: can the Mediterranean paradox be explained? A systematic review

Spyridon Karras[1], Stavroula A Paschou[1], Eleni Kandaraki[1], Panagiotis Anagnostis[1], Cédric Annweiler[2,3], Basil C Tarlatzis[1], Bruce W Hollis[4], William B Grant[5] & Dimitrios G Goulis[1]
[1]Unit of Reproductive Endocrinology, First Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece; [2]Department of Geriatric Medicine, University Hospital, Angers, France; [3]Department of Medical Biophysics, Robarts Research Institute, Schulich School of Medicine and Dentistry, University of Western Ontario, Ontario, Canada; [4]Medical University of South Carolina Children's Hospital, Charleston, South Carolina, USA; [5]Sunlight, Nutrition, and Health Research Center, San Francisco, California, USA.

Introduction
Despite high levels of sunshine, maternal hypovitaminosis D during pregnancy is prevalent in the Mediterranean region, consisting a paradox. The aim of the study was to systematically review trials that investigated vitamin D concentrations during pregnancy in this region, in order to determine predictors of hypovitaminosis D and explain the paradox.
Methods
After applying inclusion/exclusion criteria, 15 studies were entered into the systematic review, involving 2649 pregnant women and 1820 neonates. The main outcome was maternal vitamin D concentration. Possible predictors of the outcome included study, maternal and neonatal characteristics (age, BMI, race, socioeconomic status, skin type, gestational age, sun exposure, calcium and vitamin D intake and supplementation, smoking status, parity, season of delivery, pregnancy complications).
Results
Studies differed widely in vitamin D deficiency criteria, methods of measurement and outcomes. However, prevalence of maternal and neonatal hypovitaminosis D was up to 90%. Predictors of maternal hypovitaminosis D were dark skin phototype, race and sartorial habits. Only a few pregnant women met the recommended dietary daily intake of calcium and vitamin D. Vitamin D supplementation was not a common practice.

Conclusions
Hypovitaminosis D during pregnancy is prevalent in the Mediterranean region. Racial, social and cultural habits, as well as the absence of preventive strategies seem to negate the benefits of sun exposure.

DOI: 10.1530/endoabs.37.EP241

EP242

Association between BMI and femoral neck bone mineral density in post-menopausal women: analysis of NHANES cross sectional data 2008–2012

Sangeeta Chandramahanti, Henry Driscoll, Adenrele Olajide, Omolola Olajide, Ralph Webb & Prasanna Santhanam
Joan C Edwards School of Medicine, Marshall University, Huntington, West Virginia, USA.

Introduction
Obesity was thought to be protective against osteoporosis, but studies have shown conflicting results. We analysed the cross-sectional data from the National Health and Nutrition Examination Survey Data (NHANES) survey (2008–2012) to observe the association between BMI (BMI and/or waist circumference) and bone mineral density (BMD) at the femoral neck.
Research methods and design
We categorised the study population (women aged 50 years and above) into three groups based on their BMI- lean (BMI <18.5 kg/m^2), normal (BMI between 18.6–24.9 kg/m^2), and overweight/obese (BMI >25 kg/m^2). We reviewed and tabulated data on the demographics (age, race and other covariates), waist circumference (cm), mean systolic BP (mm/Hg), HOMA insulin resistance, and total cholesterol (mg/dl). We analysed the data on femoral neck BMD (gm/cm^2), total femur BMD, femoral neck bone mineral content (BMC in gm) and total femur BMC. We used the one-way ANOVA to test the difference between the groups. We also performed a correlation (non-parametric spearman's ρ) between BMI and femoral neck BMD and waist circumference and femoral neck BMD.
Results
There were 1071 persons in the cohort. There was no significant difference in BMD or BMC between the groups at the femoral neck ($P=0.39$, $P=0.79$ respectively) or total femur ($P=0.75$, $P=0.86$ respectively). Systolic blood pressure was higher in obese/overweight women ($P<0.01$). There was no correlation between femoral neck BMD and BMI (spearman's $\rho -0.07$, $P=0.25$) or femoral neck BMD and waist circumference (spearman $\rho -0.09$, $P=0.14$).
Conclusions
Our results shows that BMI and waist circumference are not associated with differences in femoral neck BMD in post-menopausal women.

DOI: 10.1530/endoabs.37.EP242

EP243

The response to teriparatide of a patient with β-thalassemia and multiple endocrine complications

Luminita-Nicoleta Cima[1,3], Alice Albu[2,3], Ioana Lambrescu[1,3], Carmen Gabriela Barbu[2,3] & Simona Fica[2,3]
[1]Babes Institute, Sectorial Operational Programme Human Resources Development (SOPHRD), financed by the European Social Fund and the Romanian Government under the contract number POSDRU 141531, Bucharest, Romania; [2]Elias Hospital, Bucharest, Romania; [3]'Carol Davila' University of Medicine and Pharmacy, Bucharest, Romania.

Introduction
Osteopenia/osteoporosis in young adults with β-thalassemia major (BTM) is a prominent cause of morbidity despite adequate transfusion and iron chelation therapy. The reported frequency of osteoporosis, even in well treated TM patients varies from 13.6% to 50%, with an additional 45% affected by osteopenia.
Case report
We present the case of a 36-years-old male patient with BTM treated for 1 year with teriparatide for osteoporosis. Our patient was diagnosed with BTM at 6 months of age and he was treated with chronic blood transfusions since that moment associated intermittently with chelation therapy due to limited availability and lack of compliance of the patient. From his medical history we mention splenectomy at the age of 3, iron overload-related liver disease, chronic hepatitis C, cardiomegaly (hemosiderosis), femural dyaphysis fracture (1992), hypogonadotropic hypogonadism, secondary diabetes mellitus (2008), and hyperparathyroidism (2009). For his endocrine complications he received substitutive treatment with testosterone undecanoate, calcium, vitamin D and insulin. In January 2009 he was diagnosed with severe osteoporosis with multiple vertebral fractures, he had vertebroplasty performed at T11 and T12; alendronate treatment was initiated until November 2013 when a new vertebral fracture occurred at L5. In this context, the alendronate treatment was considered suboptimal/ineffective; therefore, therapy with rPTH was initiated. After 1 year of therapy with teriparatide his DXA measured lumbar spine BMD significantly improved (9.8% increment) without any signs of a new fracture.
Conclusions
The osteoporosis in BTM has a complex mechanism; both increased bone resorption and decreased formation being involved. Probably the extent of contribution of the two mechanisms varies in each patient. Although the bisphosphonates are the most used treatment for osteoporosis in BTM, our case report suggests that, at least in some patients, decreased bone formation is the predominant mechanism and teriparatidum could be the most appropriate therapy.
Disclosure
This paper is partly supported by the Sectorial Operational Programme Human Resources Development (SOPHRD), financed by the European Social Fund and the Romanian Government under the contract number POSDRU 141531.

DOI: 10.1530/endoabs.37.EP243

EP244

Quick PTH improves the cure rate of minimally invasive surgery in patients with primary hyperparathyroidism and preoperative localized parathyroid adenoma

Cristian Velicescu, Alina Gatu, Radu Danila, Alexandru Grigorovici & Voichita Mogos
University of Medicine and Pharmacy 'Gr.T.Popa', Iasi, Romania.

Introduction
Intraoperative quick PTH (iqPTH) monitoring is important in the treatment of primary hyperparathyroidism (pHPTH), allowing, together with preoperative localisation, the switch from routine bilateral neck exploration to limited gland excision.
Aims
We checked the advantage of iqPTH for improving the cure rate of patients operated for pHPTH by using minimally invasive surgery (MIS).
Materials and methods
Retrospective study comparing two groups of patients with pHPTH caused by isolated sporadic parathyroid adenomas localised before surgery with sesta-MIBI scintigraphy and ultrasound. All patients were operated by MIS. Adenoma excision was histologically confirmed. The 40 patients from the first group (control, C) were operated without measuring iqPTH, whereas iqPTH and serum calcium were assessed in the second group (iqPTH) of 13 patients 5 min after the excision of the adenoma and before wound suture. When iqPTH dropped $<50\%$ the pre-excision value, MIS was converted to open neck surgery.
Results
Six out of the 40 patients from the C group (15%) had persistent hypercalcemia and elevated PTH at 24 h, 3 and 6 months after surgery, needing reintervention. Eleven out of the 13 patients from the iqPTH group had an important drop of iqPTH after adenoma excision, whereas two of them (15.4%) persisted having high iqPTH levels. Conversion to open neck surgery allowed localising a preoperatory undetected supplementary parathyroid adenoma in both cases. Excision of the second adenoma allowed PTH normalization and cure in only one surgical intervention, thereby increasing success rate to 100% in the iqPTH group ($P<0.05$).
Conclusion
The addition of an iqPTH assay to MIS provides a quick and reliable intraoperative confirmation of accurate adenoma removal. iqPTH is able to distinguish between single and multiple gland disease. Persistence of high iqPTH indicates conversion to bilateral neck exploration, thereby increasing cure rate in the same intervention.
Disclosure
This work was supported by the European Social Found, Human Resources Development Operational Programme 2007–2013, project no. POSDRU/159/1.5/S/136893.

DOI: 10.1530/endoabs.37.EP244

EP245

A rare cause of increased bone mineral density in adulthood: autosomal dominant osteopetrosis

Yuksel Altuntas, Feyza Yener Ozturk, Idris Kuzu, M Masum Canat, Savas Karatas & Sezin Dogan Cakir
Sisli Hamidiye Etfal Training and Research Hospital Department of Endocrinology and Metabolism, Istanbul, Turkey.

Introduction and aim
Osteopetrosis is a rare genetic disorder of reduced osteoclastic bone resorption. Defective bone remodelling induces skeletal sclerosis and abnormally dense but brittle bones. We present here a case of autosomal dominant osteopetrosis type II as a cause of high bone mineral density (BMD).
Case report
A 52-years-old woman with a complaint of bone pain and headache referred to our clinic for evaluation of high BMD. Her medical history and physical examination were unremarkable. Increased BMD in DXA scanning affecting both spine and hip was classified as generalised and acquired causes were evaluated initially. Serum fluoride concentration, renal and liver function tests, IGF-1 level, hepatitis C serology were all normal excluding fluorosis, renal osteodystrophy, acromegaly, hepatitis C associated osteosclerosis. There was no splenomegaly or hematologic abnormality for miyelofibrosis. Serum tryptase level was normal excluding mastocytosis. She denied any usage of oestrogen implants. Excluding the acquired causes, the specific features suggesting monogenic disorders such as osteopetrosis or sclerosing bone dysplasias were investigated. Rugger-jersey spine due to vertebral end plate thickening, bone within bone in pelvis and transverse sclerotic bands within distal femur, the classic signs of osteopetrosis, were recognized at plain radiographs. She denied any history of fracture and also, whole body radiographic survey showed no pathological fractures. Her serum acid phophatase was high. She was diagnosed as adult type osteopetrosis type II. Complication screening revealed only mild decrease in high-pitched voice in audiology.
Conclusion
Autosomal dominant osteopetrosis exhibits a heterogeneous trait with milder symptoms, often diagnosed at later adolescence or adulthood. Two distinct types (type I and II) have been described on the basis of radiographic, biochemical and clinical features. Type II disease appears to increase the risk of fracture. The disease requires no treatment although the complications may require intervention.

DOI: 10.1530/endoabs.37.EP245

EP246

Hypocalcaemia due to 22q11.2 deletion syndrome diagnosed in adulthood

Maria Cabrer Vidal, Guillermo Serra Soler, Marzena Wos, María Soledad Gogorza Pérez, Iñaki Argüelles Jiménez, Santiago Tofé Povedano, Elena Mena Ribas, Honorato García Fernández & Vicente Pereg Macazaga
Hospital Universitari Son Espases, Palma de Mallorca, Spain.

Introduction
Hypocalcaemia is present in half of the patients with 22q11.2 deletion syndrome (DiGeorge-velocardiofacial syndrome). Most of these cases are diagnosed during childhood.
Case report
A 56-year-old man was evaluated for symptomatic hypocalcaemia after undergoing a left nephrectomy because of renal tumour. He had paraesthesia around his mouth and hands and Trousseau's sign. His past medical history included high blood pressure, type 2 diabetes, dyslipidaemia and chronic obstructive pulmonary disease. He mentioned a hypocalcaemia episode 10 years ago, frequent bronchitis at childhood and learning difficulties. Blood tests showed hypocalcaemia of 6.2 mg/dl (NV: 8.4–10.2) hypoalbuminaemia of 29.7g/l, (35–50 g/l), corrected calcium of 7.08 mg/dl, hyperphosphataemia of 4.8 mg/dl (2.3–4.7) and normal magnesium. Parathyroid hormone (PTH) was 11 pg/ml (15–88), 25-hydroxy vitamin D 16 pg/ml (>30) and 1.25-dihydroxy vitamin D 20.1 pg/ml (26.1–95). Thyroid function was normal. The electrocardiogram showed no prolonged QT interval. Endovenous and oral calcium and calcitriol were initiated, with normalization of calcium levels. Based on hypocalcaemia secondary to primary hypoparathyroidism anti-parathyroid antibodies and anti-calcium sensor receptor were requested. Due to childhood medical history and dysmorphic phenotype (hooded eyelid, bulbous nasal tip) a genetic test of 22q11.2 deletion was made. Anti-parathyroid antibodies were negative, anti-calcium sensor receptor antibodies finally were not made and the genetic test confirmed the diagnosis, so more tests were made in the outpatient clinic. Treatment at discharge was oral calcium and calcitriol. Echocardiography was normal. Densitometry revealed no bone mass loss. Immunologic studies showed a mild disturbance of cellular immunity. He received genetic advice of affected offspring.
Conclusions
It is important to classify hypocalcaemia diagnosed at any age, and especially hypocalcaemia due to genetic syndromes, as in our case, due to the 50% risk of an affected offspring.

DOI: 10.1530/endoabs.37.EP246

EP247

Clinical and biochemical response to denosumab in a young adult patient with craniofacial fibrous dysplasia

Elisa Cairoli[1], Cristina Eller-Vainicher[1], Diego Sergio Rossi[2], Giada Anna Beltramini[2], Antonio Russillo[2], Giovanna Mantovani[1], Anna Spada[1] & Iacopo Chiodini[1]
[1]Unit of Endocrinology and Metabolic Diseases, Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; [2]Department of Maxillofacial Surgery and Odontostomatology, Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, University of Milan, Milan, Italy.

We report on the clinical and biochemical outcomes in a 20-year-old male suffering from active craniofacial monostotic fibrous dysplasia (MFD) treated with the RANK-L inhibitor, Denosumab, following unsatisfactory responses to prior long-term bisphosphonates therapy. The patient had been treated over 9 years with pamidronate (cumulative dose of 81 mg), but experienced only mild reductions in pain scores. Following initiation of Denosumab 60 mg subcutaneously, bone pain and bone turnover markers (osteocalcin, total and bone alkaline phosphatase and β-crosslaps) were monitored over a period of 14 months. Following the first administration, the patient demonstrated a promptly and pronounced clinical and biochemical response: within few hours the patient reported pain disappearance and after 4 weeks bone turnover markers fell to levels within the normal range. Three months after initiation of Denosumab the patient reported an acute pain reactivation that required a second administration. As previously, after few hours the pain disappeared. Later Denosumab was administered according to pain reappearance and the injections were always followed by complete pain relief. However, a gradual shortening of the pain-free interval between administrations was observed, ranging from 90 days after the first one to 75 days after the fifth one. Treatment with Denosumab was always well tolerated. The monitoring of bone turnover showed that all markers stayed in the lower half of the normal range, even at the moment of pain reappearance, suggesting that the effect of Denosumab on pain depends on mechanisms other than bone resorption suppression.
In conclusion, Denosumab appears to be effective in reducing bone turnover and bone pain in adult patients with active MFD and could represent a good alternative to bisphosphonates, allowing to avoid elevate cumulative doses of these agents. Further studies are required to clarify the efficacy, safety and mechanisms of long-term therapeutic RANK-L inhibition in MFD.

DOI: 10.1530/endoabs.37.EP247

EP248

Hypophosphataemic rickets: two unrelated Mexican female cases and review of the literature

Nory Omayra Davalos[1,2], Ruth Minerva Martínez[3], Jose de Jesus Magallanes-Ordoñez[4], Celia Andrea Ramírez-Aréchiga[5], Enrique Cervantes-Pérez[6], J F Michel Monrroy[7] & J Fonseca Cárdenas[7]
[1]Instituto de Genética Humana Dr. Enrique Corona, Doctorado de Genética Humana, CUCS, Universidad de Guadalajara, Guadalajara, Mexico; [2]Servicio de Genética, HRVGF ISSSTE, Zapopan, Mexico; [3]Endocrinología, HRVGF ISSSTE, Zapopan, Mexico; [4]Cirugia Plastica y Reconstructiva, HRVGF ISSSTE, Zapopan, Mexico; [5]CORENTE, Instituto Especializado en la CorInteligencia S.C, Zapopan, Mexico; [6]Departamento de Bienestar y Desarrollo Sustentable Centro Universitario del Norte U de G, Colotlán, Mexico; [7]Ortopedia y traumatología, HRVGF ISSSTE, Zapopan, Mexico.

Introduction
Hypophosphataemic rickets (HR) is a rare genetic disorder characterized by poor growth, short desproporcionate stature and lower limb anomalies.

Clinical manifestations usually appear before 1 year of age, this entity is characterised by osseus hypomineralisation, secondary to the increased expression of phosphatonins, especially FGF23, which acts in the sodium and phosphate co-transporters of the proximal convoluted tubule, inducing phosphaturia. HR exhibits AD, AR or X-linked inheritance patterns.
Objective
We present two unrelated HR case reports, with clinical radiological and laboratory studies of Hypophospataemic Rickets with osseous complications and adverse medical events.
Case reports
Case 1: 7.6-year-old girl, physical examination showed height 113 cm, weight 24 kg, arm spam 116 cm, OFC 48 cm, with disproportional short stature, *genu varo*, gait difficulties, asymmetric thorax; actually presenting normocalcaemic, normophosphataemia, phosphaturia, calcitriol deficiency and secondary hyperparathyroidism.
Case 2
15-year-old girl at physical examination showed height 141 cm, weight 76 kg, with surgical antecedents, the first one in order to correct bilateral tibia deformity at age 3, and genu varum correction surgery at age 5; actually presents recidivant *genu varo*, normocalcaemic, hypophosphataemia, and phosphaturia.
Discussion
Hypophosphataemic rickets should be suspected in any child with disproportionate short stature, developmental delay and short, malformed legs. Only one-third are due to nutritional deficit, clinical cases presented meet clinical criteria and radiological rickets. In case 1 presents normocalcaemic, normophosphataemia indicating good control in the treatment. The case 2 has normocalcaemia, hypophosphatemia and vitamin D insufficiency, renal presenting microlithiasis and secondary hyperparathyroidism, which suggests a more aggressive disease character.
Conclusions
Due to functional complications in HR, early diagnosis and treatment is necessary, based in growth curves as well as serum values of phosphorus, calcitriol, alkaline phosphatase, and others, in order to offer an optimal medical care and prevent secondary osseous deformities.

DOI: 10.1530/endoabs.37.EP248

EP249

Analytical evaluation of a new fully automated immunoassay for the quantification of 1,25-dihydroxyvitamin D

Nathalie Miller & Damien Gruson
Cliniques Universitaires St Luc, Brussels, Belgium.

Background
Quantification of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) remains challenging because of low circulating concentrations and potent cross-reactivities with steroid-like structures. The most frequent assays for $1,25(OH)_2D$ testing are still based on RIA format with preliminary extraction. The analytical performances and the turnaround time of analysis (TAT) for these assays are limited. Several novel assays for $1,25(OH)_2D$ testing are emerging. The aim of our study was therefore to evaluate the analytical performances of a recently developed automated immunoassay for the measurement of $1,25(OH)_2D$.
Methods
We evaluated the performances of the LIAISON XL $1,25(OH)_2D$ assay (DiaSorin), a fully automated immunoassay that uses a recombinant fusion protein for capturing $1,25(OH)_2D$. The limit of detection and the within- and between-run imprecision were determined. Method comparison was performed with our routine RIA method and with a reference Liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.
Results
The limit of detection was <5 pg/ml. The within-run coefficients of variation (CV) were 2.6 and 4.4% for $1,25(OH)_2D$ concentrations of 6.7 and 19.7 pg/ml and the between run CVs were 9.3 and 13.1% for concentrations of 25.4 and 101.1 pg/ml. The automated $1,25(OH)_2D$ assay was significantly correlated to RIA ($r=0.74$; $P<0.0001$) and LC-MS/MS ($r=0.9975$; $P<0.0001$). The comparison of the automated assay and RIA revealed through Passing-Bablok regression analysis a slope of 0.86 and an intercept of 14.12. The mean bias observed on the Bland-Altman plot was -2.8 pg/ml. The comparison of automated assay and LC-MS/MS revealed through Passing-Bablok regression analysis a slope of 1.07 and an intercept of -1.87. The mean bias observed on the Bland-Altman plot was -8.2 pg/ml.
Conclusion
The LIAISON XL $1,25(OH)_2D$ automated assay demonstrated superior analytical performances in comparison to RIA assay and a clear improvement of TAT. Furthermore, we demonstrated a strong agreement between this $1,25(OH)_2D$ automated assay and a reference LC-MS/MS method.

DOI: 10.1530/endoabs.37.EP249

EP250

High offset point for normocalcaemic secondary hyperparathyroidism due to vitamin D deficiency

Taimur Gulfam, Naveen Aggarwal, Murali Ganguri & Richard Quinton
Department of Endocrinology, Royal Victoria Infirmary, Newcastle Upon Tyne, UK.

Introduction
Vitamin D deficiency occurs more frequently in patients with primary hyperparathyroidism compared to general population, and is usually associated with an aggravated form of the disease. Current guidelines recommend measurement of vitamin D level in all patients with primary hyperparathyroidism, and their repletion if the levels are <50 nmol/l.
Case report
We present a 56 years old Caucasian lady who underwent right parathyroidectomy & thyroid lobectomy for right parathyroid carcinoma in 1998. Her initial serum parathyroid level was 48.2 pmol/l (1.1–6.4). Postoperatively, her parathyroid level improved to 7.5 pmol/l but never came back to normal. She was followed up in endocrine clinic for persistent normocalcaemic hyperparathyroidism with no evidence of recurrent parathyroid cancer. In January 2010 her parathyroid level was 7.8 pmol/l with concomitant vitamin D level being 80 nmol/l (>50 nmol/l). She was started on ergocalciferol 400 IU twice daily. After 6 months, her parathyroid levels were 4.3 pmol/l which suggested secondary hyperparathyroidism due to relative vitamin D deficiency. In March 2012, despite being on vitamin D supplementation, her parathyroid levels were elevated at 6.6 pmol/l with vitamin D level being 86 nmol/l. She was advised to continue with same dose of vitamin D supplement. In March 2014, her parathyroid level increased further to 8.6 nmol/l with her being vitamin D replete at 107 nmol/l. This time it was decided to increase the dose of vitamin D to 2000 IU/day. After 6 months of treatment with increased dose of vitamin D, her parathyroid level normalized to 4.6 pmol/l with vitamin D levels of 152 nmol/l. She was normocalcaemic during all this time.
Discussion
In this patient, her parathyroid levels normalised after achieving a vitamin D level, which was higher then usually recommended level. In selected patients, we may need to aim for a higher vitamin D level before seeing an improvement in parathyroid levels.

DOI: 10.1530/endoabs.37.EP250

EP251

Low bone mass in Sheehan's syndrome: prevalence and management

Melika Chihaoui, Dhouha Ben Salah, Meriem Yazidi, Fatma Chaker, Bochra Ftouhi & Hedia Slimane
University Hospital la rabta, Tunis, Tunisia.

Introduction
Hypopituitarism is a known cause of bone mineral loss. Our study aimed to evaluate the frequency of osteopenia and osteoporosis in patients with Sheehan's syndrome and to evaluate its management.
Subjects and methods
It is a retrospective longitudinal study concerning 60 cases of Sheehan's syndrome that have had a bone mineral density measurement. The parameters of osteodensitometry, the received treatment and the follow up data were collected. The baseline parameters of osteodensitometry were compared to those of 60 age-, height- and weight- matched healthy control women.
Results
The mean age at osteodensitometry measurement was 49.4 ± 9.9 years (range 25–76 years). Osteopenia was present in 25 patients (41.7%) and osteoporosis in 23 (38.3%). Bone mineral density was significantly lower than in the control group ($P<0.001$). The odds-ratio of osteopenia-osteoporosis was 6.3. Low bone mineral mass concerned more frequently lumbar spine ($P<0.05$). Bone fracture was reported by three patients (5%). Only six of the osteoporotic patients were treated with bisphosphonates. Osteodensitometry was controlled in 15 cases after a mean duration of 6 years and showed an improvement in four cases.

Conclusion
Low bone mineral mass was very frequent in patients with Sheehan's syndrome. Treatment was insufficient.

DOI: 10.1530/endoabs.37.EP251

EP252

Comparison of the pre-operative and post-operative haemogram parameters of the patients with primary hyperparathyroidism

Ulku Aybuke Tunc[1,2], Tevfik Demir[1,2], Merve Yilmaz[1,2] & Arzu Gedik[1,2]
[1]TEMD, Turkey; [2]The Endocrine Society, USA.

Anaemia prevalence is reported between 5 and 31.8% in patients with PHPT. Anaemia in PHPT shows correlations with serum calcium, PTH, alkaline phosphatase levels, severity of the bone disease and PHPT duration. In this study we compared pre-operative and post-operative haemogram parameters of patients with PHPT who received a parathyroidectomy at our department. We determined the prevelance of pre-operative anaemia, thrombocytopenia, neutropenia and observed if any of this parameters were recovered after the surgery. We excluded patients with systemic diseases which may interfere with cytopenias. Likewise, we determined pre-operative and post-operative variations of some parameters such as RDW, MPV, neutrophile/lymphocyte rates, that are often disregarded in haemogram reports but related to chronical inflammation. Out of 157 patients with PHPT, 127 (80.9%) were women and 30 (19.1%) were men. There was no significant difference in terms of prevalence of cytopenia before and after the surgery for PHPT. Correlation analysis did not reveal any significant differences between studied parameters except that there was a moderate-weak relation between PTH level and neutrophile/lymphocyte rate. Mean RDW was high in patients with PHPT before the surgery, however it did not improve after the operation significantly. There are no studies in the literature evaluating RDW, MPV values and neutrophile/lymphocyte rates that are related to primary hyperparathyroidism (or secondary, tertiary hyperparathyroidism). Our study has the feature of being the first study in this field, more significant data is expected to be obtained as the number of included patients increase.

DOI: 10.1530/endoabs.37.EP252

EP253

TSH and free-T_3 correlate negatively and independently with bone mineral density in adults with subclinical hypothyroidism

Anna de Lloyd[1], Ilaria Muller[1], Alan Dodd[2], Hilary Durrant[2], Rebecca Pettit[3], Sarah Darlington[3], Lei Zhang[1], Carol Evans[2], Aled Rees[1] & Marian Ludgate[1]
[1]Thyroid Research Group, IMEM, Cardiff University, Cardiff, Wales, UK; [2]Department of Medical Biochemistry and Immunology, University Hospital of Wales, Cardiff, Wales, UK; [3]Department of Medical Physics, University Hospital of Wales, Cardiff, Wales, UK.

The role of the thyrotropin receptor (TSHR) in bone is unclear. TSHR-deficient mice have low bone mineral density (BMD) and focal osteosclerosis despite normal thyroid hormones (suggesting TSHR function, in bone, is important). Subclinical hypothyroidism (SH) has various aetiologies including thyroid autoimmunity (TA) and inactivating TSHR mutations (TSHR-M). In TSHR-deficiency & TSH-M elevated TSH compensates for reduced TSHR function, whereas in TA it compensates for reduced thyroid synthetic responsiveness (inflammation mediated). We hypothesised differential bone effects in SH relating to these causes.
Aims
i) To establish whether free-T_4, free-T_3 or TSH are associated with BMD and bone turnover (BT) in SH. ii) To explore whether SH aetiology influences BMD and BT.
Methods
208 adults with primary untreated SH (TSH$\geqq$5 mU/l) and free of known bone disease were recruited. A medical/lifestyle history, anthropometric data and blood samples were collected (free-T_3, free-T_4, TSH, anti-TPO antibodies, BT markers (CTX, P1NP)). Mutational screening of the entire TSHR coding region was undertaken by dHPLC and confirmed by direct sequencing. A DXA bone scan (lumbar spine (LS) and hip) generated *Z*-scores (relative to age/sex-matched normals (BMD-Z)) which were evaluated alongside thyroid parameters in stepwise multivariate regression analyses.
Results
50% of the cohort were TPO+ and 6% had TSHR-Ms. After adjustment for potential confounders, TSH associated negatively with BMD-Z at the LS ($R=-1.7$, $P<0.001$) whereas free-T_3 associated negatively with BMD-Z at both sites (hip: $R=-0.35$, $P=0.005$; LS: $R=-0.5$, $P=0.002$) and free-T_4 showed no independent associations. Stratification by SH aetiology showed no influence of TSHR-M on BMD-Z (despite lower free-T_3 relative to TSH ($R=-0.34$, $P=0.01$) but TPO+ associated negatively with BMD-Z at the LS ($R=-0.65$, $P<0.001$). Male gender associated negatively with BMD-Z at all sites ($R=-0.8$, $P=0.001$). BT markers did not associate with thyroid function or BMD.
Conclusions
In adults with SH, BMD is associated negatively with free-T_3, TSH, male gender and TPO antibody positivity.
Disclosure
Society for endocrinology grant

DOI: 10.1530/endoabs.37.EP253

EP254

Vitamin D deficiency in patients with autoimmune thyroiditis

Ivan Pankiv
Bukovinian Medical Univetsity, Chernivtsi, Ukraine.

There is increasing interest in the role of vitamin D deficiency in a number of chronic health problems including autoimmune diseases. The aetiology and pathogenesis of most autoimmune disorders remain obscure and a number of factors have been implicated in their pathogenesis, one of the most recent agents found to be associated with autoimmunity is vitamin 25(OH)D. The aim of the study was to assess total vitamin 25(OH)D status in patients with autoimmune thyroiditis with subclinical and overt hypothyroidism.
Methods and materials
70 patients (54 females and 16 males) and 20 apparently healthy individuals with matched age and sex were underwent a detailed clinical examination, thyroid function tests (TSH, fT_4, fT_3, thyroid peroxidase antibodies) and serum total vitamin 25(OH)D.
Results
The patient group with autoimmune thyroiditis was classified according to the level of TSH into subclinical and overt hypothyroid groups. Levels of serum TSH were significantly increased in subclinical (6.80 ± 1.84 μIU/ml) and hypothyroid (10.24 ± 2.09 μIU/ml) groups as compared to control group (2.16 ± 0.39 μIU/ml) ($P<0.05$). The thyroid peroxidase antibodies level was 312.83 ± 7.19 IU/ml in subclinical hypothyroid group and was 529.31 ± 9.62 IU/ml in the hypothyroid group. The levels of serum total 25(OH)D were significantly decreased in subclinical (18.8 ± 1.2 nmol/l) and overt hypothyroid groups (21.9 ± 1.1 nmol/l) as compared to control group (27.1 ± 1.2 nmol/l), ($P<0.05$). A highly significant negative correlation was found between serum TSH, thyroid peroxidase antibodies and total 25(OH)D levels ($P<0.001$). Also highly significant positive correlation was found between the levels of serum total 25(OH)D and serum fT_4 ($P<0.001$). There was significant positive correlation between TSH and thyroid peroxidase antibodies levels ($P<0.05$).

DOI: 10.1530/endoabs.37.EP254

EP255

PTH 1–34 replacement therapy in post-surgical hypoparathyroidism: preliminary results from the 6-month follow up study

Antonella Franchi, Valentina Congedo, Doris Tina, Gianmarco Raggiunti, Giuseppe Fiore & Bruno Raggiunti
Endocrinology and Metabolic Desease Unit, Atri Hospital, Atri, Abruzzo, Italy.

Hypoparathyroidism is characterised by parathyroid hormone (PTH) levels inadequate to maintain plasma calcium concentration within the normal range. Even if the conventional treatment with calcium supplements and active vitamin D analogues is usually able to maintain normocalcemia, episodic low plasma calcium, neuromuscular complaints, renal disease and gastric discomfort are not infrequent. 29 patients with post-surgical hypoparathyroidism were started on PTH 1–34 therapy, because of persistent low plasma calcium, related to low calcium intake due to calcium intolerance and decreased quality of life (QoL). The still ongoing protocol includes periodic visits with biochemical exams,

quantitative ultrasound of calcaneus (QUS) and a questionnaire to assess QoL. We present the preliminary data on the 14 patients (12 females, mean age: 60.7 ± 9.29 years old), who have completed the 6-month follow up, reaching the 1-year visit in six cases. At the baseline, the mean plasma calcium was 7.68 ± 0.68 mg/dl (normal range: 8.6–10.2) and the mean 24-h urinary calcium was 218.71 ± 161.4 mg/dl (normal range: 100–300). PTH 1–34 was added at an initial dose of 0.5–0.7 μg/kg (~20–80 μg/die), twice a day. The PTH 1–34 and vitamin D analogues were titrated based on clinical and biochemical results, while the calcium supplements were progressively stopped in all patients. At the 6-month follow up, the mean plasma calcium was 8.84 ± 0.93 mg/dl (+15%) and the mean 24-h urinary calcium was 267.36 ± 98.3 mg/dl (+22%). The QoL had improved in all patients. The muscular pain, referred in three patients, was the most common complaint, causing a temporary discontinuation of PTH 1–34 only in one case. No serious adverse events were reported. These preliminary results have confirmed the efficacy and safety of PTH 1–34 in post-surgical hypoparathyroidism. The ongoing follow up will define the long-term effects of PTH 1–34-RT.

DOI: 10.1530/endoabs.37.EP255

EP256

Vitamin D is essential for the musculoskeletal health, its effect being independent of age, menopause or PTH level: our study aims to find the threshold of 25OH-D, suggestive for osteoporosis

Dana Stoian[1], Mihaela Craciunescu[2], Marius Craina[1] & Bogdan Timar[3]
[1]Department of Obstetrics Gynecology, Victor Babes University of Medicine, Timisoara, Romania; [2]Department of Microbiology, Victor Babes University of Medicine, Timisoara, Romania; [3]Department of Medical Informatics, Victor Babes University, Timisoara, Romania.

We evaluated 341 postmenopausal women, aged 29–84 years (mean age 58.18 ± 9.01) and referred to the Center for Osteoporosis starting December 2013. Secondary causes of osteoporosis/bone loss and patients under antiosteoporotic medication or under vitamin D substitution were excluded from the study. All patients performed DXA measurement (Dexxum T, Osteosys, Inc., South Korea) (same expert). FRAX and 25 HO vitamin D levels were determined. We defined vitamin D deficiency as levels below 10 ng/ml and insufficiency as levels below 30 ng/ml. The mean 25 HO vitamin D value in the investigated group was 23.69 ± 11.40 ng/ml (4.1–71.3 ng/ml). Vitamin D insufficiency was present in 65.39% and deficiency in 9.38% of the cases. The level of deficiency/insufficiency increased with age, but was described even in young woman (below 40). When we analyzed the DXA results, the hip and spine density turned out to be lower in the presence of vitamin D insufficiency. Using the ROC curve and Youden index, we observed that a 25 HO vitamin D level lower than 21.80 ng/ml is highly predictive for lumbar and femoral neck demineralisation.

Conclusion

Evaluation of vitamin D status is important in the assessment of bone health in postmenopausal women, decreased levels of vitamin D being associated with increased prevalence of bone demineralisation.

DOI: 10.1530/endoabs.37.EP256

EP257

Diabetes mellitus type 1

Alexander Shishkin & Victoria Manulenko
Saint Petersburg State University, Saint Petersburg, Russia.

Materials and methods

A survey was 95 people (45 people with diabetes mellitus type 1, 50 people with diabetes mellitus type 2). The age of examined patients 39.12 ± 3.8. The disease duration ranged from 6 to 20 years. Level of biochemical indicators – normal limits. Condition of mineral density of a bone tissue it was estimated by method of a dual-energy X-ray absorptiometry (DEXA). The analysis of DEXA researches showed that change of mineral density of a bone tissue at patients with diabetes of 1 type meets – 26 (57.7%), osteoporosis at 18 people (40%), osteopenia at eight people (17.7%); norm – at 19 patients (42.3%). DEXA analysis of studies in patients with type 2 diabetes showed that 21 (42.6%) patients occurs change in bone mineral density (in 8 (16%) patients – osteoporosis, 13 (26%) – diabetic osteopenia); the norm in 29 (58%). Our analysis showed that for patients with diabetes mellitus type 1 the most characteristic changes of DEXA parameters in three standard areas of study. While for patients with diabetes mellitus type 2 is characterized by changes in mineral density of bone tissue in two standard zones of the study. As well as that of patients with diabetes mellitus types 1 and 2 changes in mineral density of bone tissue previously only detected in the lumbar spine. In patients with diabetes mellitus types 1 and 2 was positive correlation between the duration of diabetes, diabetes compensation, the presence of diabetes complications and bone mineral density ($P < 0.05$).

DOI: 10.1530/endoabs.37.EP257

EP258

Primary hyperparathyroidism with negative pre-operative imaging: a review of current and emerging localisation modalities

Zhi Guang Ng & Cherng Jye Seow
Tan Tock Seng Hospital, Singapore, Singapore.

Introduction

Primary hyperparathyroidism (PHPT) is usually caused by a single hyperfunctioning parathyroid adenoma. Preoperative localization studies allow for minimally invasive surgical removal. We present a case of PHPT caused by a solitary adenoma that could not be localised pre-operatively and review existing and emerging localisation modalities.

Case report

A 65-year-old Chinese lady admitted for neck of femur fracture was found to have hypercalcaemia of 2.82 mmol/l (RI: 2.15–2.58 mmol/l) and PTH level of 16.2 pmol/l (RI: 0.8–6.8 pmol/l). History was unremarkable for renal impairment, drug related causes or malignancy. Her calcium/creatinine clearance ratio of 2.12% was suggestive of PHPT. Ultrasonography did not localize any hypoechoeic ovoid structures but showed multiple thyroid nodules. Fine needle aspiration cytology (FNAC) of the thyroid nodules was negative for malignancy. Dual tracer parathyroid scintigraphy did not reveal any sestamibi-avid or enlarged parathyroid lesion. A total thyroidectomy and exploratory parathyroidectomy subsequently revealed a right parathyroid adenoma embedded within the thyroid tissue.

Discussion

PHPT is accounted for by a solitary adenoma in 85–90% of all cases. Preoperative localization techniques allows for minimally invasive surgery which reduces morbidity. Non-invasive modalities include ultrasonography, parathyroid scintigraphy, sestamibi-single photon emission computed tomography (SPECT), 4-dimensional CT, positron emission tomography and MRI, with scintigraphy being the most sensitive (scintigraphy 54–96%, 4D-CT 88%, SPECT 79%, ultrasonography 76%, MRI 43–71%). The sensitivity of scintigraphy is decreased in four-gland hyperplasia, double adenomas or concomitant thyroid disease. The results of scintigraphy can be enhanced by combination with SPECT or using dual tracer subtraction scans. Invasive techniques such as venous PTH sampling and selective arteriography are reserved for patients with recurrent or persistent hyperparathyroidism.

Conclusion

The pre-operative localisation of a solitary adenoma in PHPT remains a challenge despite new, emerging techniques.

DOI: 10.1530/endoabs.37.EP258

EP259

Rapid and profound decrease in resorbtion markers preceded early and profound increase in BMD after successful surgery in osteitis fibrosa cystica

Daniel Grigorie[1,2], Andra Caragheorgheopol[1], Maria Iacob[1] & Alina Sucaliuc[1]
[1]National Institute of Endocrinology, Bucharest, Romania; [2]Carol Davila University of Medicine, Bucharest, Romania.

Introduction

Successful parathyroid surgery in patients with OFC leads to early and marked improvements in BMD but data on very early changes in bone markers are missing.

Case report

A 20-year-old girl was hospitalised because of severe bone pains and multiple pathological fractures (left humerus and left proximal femur) after minimal trauma. She had lost weight, was amenorrhoeic for the last 12 months and was bleeding from brown tumours in her mouth. She was unable to walk and was

complaining for general fatigue, anorexia, polyuria and polydipsia. Skeletal X-rays revealed multiple osteolytic lesions throughout the entire skeleton, brown tumours in the mandible and OFC change of the left shoulder. Serum calcium and PTH were of 14.7 mg/dl and 1243 pg/ml, respectively; alkaline phosphatase activity was 1372 U/l. After hydration with i.v. sodium chloride, the patient was given i.v. pamidronate (60 mg) and serum Ca fell to 12.4 after 2 days. The patient underwent parathyroid surgery and a right superior parathyroid adenoma (2.2 g) was removed. She was treated with oral calcium carbonate (2.4 g daily) and cholecalciferol 2000 U/daily. A marked reduction in BMD at LS (0.594 g/cm), FN (0.530 g/cm) and total body (0.680 g/cm) was seen by DXA, with *T*-scores in the markedly osteoporotic range (-4.9 and -3.9 S.D., respectively). After 9 months there were increases of 23.7, 39.6 and 31.2%, respectively; after 2 years of 44.1% (LS) and 64% (FN). In three other similar cases (OFC on X-ray) serum CTX decreased after 1 month by three to six times, while OC increased in one patient by 1.2 times and decreased in the other two by 90 and 53%, respectively. After 1 year CTX and OC were normal in the two patients with available data.

Conclusion

The cases show an unexpected rapid and profound decrease in resorbtion just 1 month after surgery while formation decreased at a much slower pace, changes that preceded the marked increase in BMD, especially at the cortical sites.

DOI: 10.1530/endoabs.37.EP259

EP260

Primary hyperparathyroidism in pregnancy: a case series

Naile Gokkaya[1], Adem Gungor[1], Arzu Bilen[2] & Habib Bilen[1]
[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, University of Ataturk, Erzurum, Turkey; [2]Department of Internal Medicine, Faculty of Medicine, University of Ataturk, Erzurum, Turkey.

Introduction

Primary hyperparathyroidism (PHP) in pregnancy is very rare condition and the true incidence of PHP in pregnancy is not well known. PHP is associated with significant maternal and foetal morbidity and mortality. PHP is diagnosed based upon levels of blood calcium and parathyroid hormone (PTH) in normal renal function status. However diagnosis of PTH can be difficult, the physiological changes of pregnancy in calcium homeostasis such as maternal blood volume expansion, hypoalbuminaemia and increased glomerular filtration rate contribute to the difficulty of PHP diagnosis during pregnancy.

Cases

We present four case reports about patients, having PHP in pregnancy. Three of patients, not to be controlled biochemically, denied the parathyroidectomy operation although they are informed about the details of their disease. They are followed up with medical therapy. The first one had no maternal or foetal complications, the second one acquired nephrolithiasis crisis in the last trimester and the third one gave a birth prematurely born baby who succumbed to tetany. The fourth patient who underwent parathyroidectomy operation in the second trimester had no maternal or foetal complications.

Conclusion

PHP in pregnancy is a preventable cause of foetal and maternal morbidity and mortality. Suspecting PHP during the pregnancy period and an early diagnosis can provide maternal and foetal well-being. During pregnancy, surgery should be avoided in the first and third trimester and conservative management should be preferred instead. Current evidence supports parathyroidectomy as the main treatment in the second trimester of pregnancy.

DOI: 10.1530/endoabs.37.EP260

EP261

Comparative effectiveness of biphosphonates and parathyroidectomy in osteoporosis related to primary hyperparathyroidism

Jersy Jair Cardenas Salas, Beatriz Barquiel Alcala, Cristina Alvarez-Escola, Beatriz Lecumberri Santamaria, Beatriz Pelegrina Cortes, Luis Felipe Pallardo Sanchez & Antonio Torrijos Eslava
Hospital Universitario La Paz, Madrid, Madrid, Spain.

Introduction

The use of Bisphosphonates could be a treatment option of osteoporosis secondary to primary hyperparathyroidism (OPHP) in patients not eligible or that refuse/reject surgery.

Methods/design

We analysed data of 46 patients diagnosed of OPHP. Fourteen underwent surgery and 32 were treated with bisphosphonates at standard dose. Densitometric parameters and of calcium-phosphorus metabolism were analyzed before and after 1 and 2 years of treatment. The analysis was performed with SPSS-20.0.

Results

There were not differences in age, BMI, menopause age, years since menopause, alcohol consumption, diagnosis of previous low-trauma fracture, calcium intake, creatinine clearance, serum PTH, urinary calcium, serum alkaline phosphatase, urinary D-pyridinoline, vitamin D; neither in the mineral density (MD) of lumbar spine, femoral neck or total hip at baseline between groups. Smoking was more frequent and serum calcium lower in the bisphosphonate group (BG) ($P<0.05$). Serum calcium and PTH decreased after 1 and 2 years of treatment within surgery group (SG) ($P<0.01$) but remained stable in the BG. Urinary calcium decreased in the SG, urine D-pyridinoline decreased in the BG and Serum alkaline phosphatase decreased in both groups after 1 and 2 years. There were no differences between groups. The lumbar spine MD increased after 1 year (0.754 ± 0.121 vs 0.785 ± 0.132; $P<0.01$) and 2 years (0.754 ± 0.121 vs 0.791 ± 0.107; $P<0.01$) in the BG, and only after 2 years (0.749 ± 0.144 vs 0.794 ± 0.189; $P<0.05$) in the SG. Femoral neck MD increased after 1 year (0.622 ± 0.091 vs 0.640 ± 0.093; $P<0.01$) but remained stable after 2 years in the BG. It also remained stable in the SG and in total hip MD in both groups. No differences were found between groups in MD in any location.

Conclusions

Bisphosphonates treatment could be as effective as parathyroidectomy in the treatment of OPHP.

DOI: 10.1530/endoabs.37.EP261

EP262

Investigating the bone metabolic parameters and serum 25-hydroxyvitamin D levels in male patients with asymptomatic hyperuricemia

Orsolya Ács[1], Emőke Csupor[2], Viktóra Ferencz[3], Szilvia Mészáros[3], Edit Tóth[4], Gábor Farkas[5] & Csaba Horváth[3]
[1]Semmelweis University School of PhD Studies, Budapest, Hungary; [2]The Health Service of Budavári Local Authorities, Budapest, Hungary; [3]1st Department of Medicine, Semmelweis University, Budapest, Hungary; [4]Department of Rheumatology, County Hospital Flór Ferenc, Kistarcsa, Hungary; [5]Centrum-Lab KFT, Budapest, Hungary.

Introduction

Over the past few years the clinical relevance of serum uric acid level has changed. The elevated serum uric acid level not only impairs the joints and the kidney function but it is also linked with an increased risk of cardivascular diseases. The aim of our study was to examine how bones are affected (change of bone mineral density (BMD), bone metabolism parameters, serum 25-hydroxy-vitamin D levels and frequency of fractures) by elevated serum uric acid level.

Materials and methods

We investigated a total of 136 patients divided into two groups according to serum uric acid level: 68 male patients with (age: 54.9 ± 1.6 years) and 68 male patients without (age: 55.2 ± 1.9 years) hyperuricemia. In all cases hyperuricemia (se level >428 μmol/l) was asymptomatic. BMD was measured by dual-energy X-ray absorptiometry (DEXA), for bone markers such as: parathyroid hormone (PTH), β-CrossLaps, 25-(OH) vitamin D3 and osteocalcin (OC) electrochemi-luminescence immunoassay was used and routine labor parameters were measured. Medical history including prevalence of bone fractures was also recorded. Statistical analysis was performed by ANOVA, with *post-hoc* Bonferroni correction (Satistica software 9.0).

Results

In patients with asymptomatic hyperuricemia lumbar spine (L2-4) BMD (*T*-score: -2.53 ± 0.20 vs -1.91 ± 0.20, $P<0.05$) and left femoral neck BMD (*T*-sc: -2.45 ± 0.16 vs -1.98 ± 0.15, $P<0.05$) were lower than in patients without hyperuricemia. Serum 25-(OH) vitamin D3 levels were also lower in the hyperuricemic group (48.4 ± 15.1 nmol/l vs 55.86 ± 16.7 nmol/l, $P<0.05$). Bone fracture had occurred in 17 of 68 hyperuricemic patients, while in the non-hyperuricemic group only seven fractures were recorded.

Conclusion

The in-time recognition and treatment of elevated serum uric acid level could positively influence the bone metabolism and be part of fracture prevention.

DOI: 10.1530/endoabs.37.EP262

EP263

Clinical outcome of patients with parathyroid gland carcinoma – single centre experience

Maja Baretic[1], Margareta Dobrenic[2], Drago Prgomet[3] & Ivana Pavlic-Renar[1]
[1]Internal Clinic, Department of Endocrinology, University Hospital Centre Zagreb, Zagreb, Croatia; [2]Clinical Department of Nuclear Medicine and Radiation Protection, University Hospital Centre Zagreb, Zagreb, Croatia; [3]Department of Ear, Nose and Throat, Head and Neck Surgery, University Hospital Centre Zagreb, Zagreb, Croatia.

Aim
To determine clinical predictors of parathyroid gland carcinoma recurrence.
Methods
We evaluated outcome of eight patients with primary hyperparathyroidism due to parathyroid carcinoma who were followed at University Hospital Centre Zagreb in period from 2004 to 2014. The median follow-up was 6 (range 2–14.5) years. Six patients (three male, three female; median age 57.5 (42–71) years) experienced long-term remission after the surgery whereas two patients had unfavourable course of the disease. In patients with remission hypercalcaemia was known in median for 4 (1–16) years before the surgery. At the time of diagnosis median PTH was 48 (24–147) pmol/l (normal value 0.2–6.7 pmol/l). All of them had renal impairment, hypertension and osteoporosis with two of them previous fractures. Following surgery hypocalcaemia rapidly developed requiring intravenous calcium replacement and prolonged hospital stay. Two female patients (age at diagnosis 31 and 32 years) had poor disease outcome. Their initial diagnosis was established on the basis of acute complication of hypercalcaemia; one of them was pregnant and her newborn had severe neonatal hypocalcaemia whereas another patient had episode of acute pancreatitis. Formerly they had no recognized comorbidities related to hypercalcaemia with the exception of osteoporosis without fractures. Their PTH values were 72 and 36 pmol/l and serum calcium concentrations 4.03 and 3.8 mmol/l respectively. Following surgery there were no clinical manifestations of hypocalcaemia and no need for intravenous calcium supplementation. Within 1 year hypercalcaemia reoccurred and metastatic disease was confirmed. In both patients multiple endocrine neoplasia was excluded and chromogranin was repeatedly negative.
Conclusion
Younger age, lack of chronic consequences of hypercalcaemia and hyperparathyroidism, no signs of sever symptomatic hypocalcaemia following surgery and no need for postoperative calcium supplementation could be clinical predictors of parathyroid gland carcinoma recurrence.

DOI: 10.1530/endoabs.37.EP263

EP264

Measuring BMD at forearm aids in diagnosing osteoporosis and identifies more patients for surgery in asymptomatic primary hyperparathyroidism

Laura Gianotti, Elena Castellano, Francesco Tassone, Micaela Pellegrino, Michela Ghio, Anna Racca & Giorgio Borretta
Division Endocrinology, Diabetology and Metabolism, Department Internal Medicine, S. Croce & Carle Hospital, Cuneo, Italy.

Introduction
Reduction in bone mineral density (BMD) is a common feature in primary hyperparathyroidism (PHPT), involving mostly cortical site. In the management of asymptomatic PHPT (aPHPT), guidelines indicate measuring BMD at lumbar spine, hip and forearm and surgery is recommended for patients with a *T*-score of −2.5 or less at one of these sites. However, BMD at forearm is not always performed.
Aim
Our aim was to evaluate the impact of measuring forearm BMD in the clinical and therapeutical management of aPHPT.
Subjects and methods
We retrospectively reviewed a prospective database of 116 patients with aPHPT at our institution between 1998 and 2013. The study cohort was identified by examining those patients who at the time of diagnosis had a dual X-ray absorptiometry (DXA) scan at all three sites. In all patients we measured PTH, total serum and ionized calcium, urinary calcium excretion, vitamin D and creatinine levels.
Results
Out of 116 patients with aPHPT we identified 13 (group A, 11.2%) who had a *T* score lower than −2.5 at forearm only, of which 6 (5.2%) possessed the criteria for surgery identified on the basis of forearm BMD only. Group B were the remaining 103 patients. Group A was older than group B (71±7.6 vs 62.7±11.8 years, $P<0.016$) while no significant difference was found in the biochemical measurements or in the BMD values at either of the other sites.
Conclusions
In our series of aPHPT, in 11.2% of patients, DXA on three sites revealed osteoporosis at forearm, but not at other sites. Among these patients, half were identified for surgery based on BMD at forearm. Except for age, these patients did not show any clinical, biochemical or BMD difference from the remaining patients. Preoperative forearm DXA increases the number of patients who meet the criteria for surgery based on BMD alone.

DOI: 10.1530/endoabs.37.EP264

EP265

Severe refractory hypocalcaemia associated with osteoblastic metastatic breast carcinoma

Vikram Lal, Simon Ashwell, Alison Humphreys & Sath Nag
James Cook University Hospital, Middlesbrough, UK.

Introduction
Hypercalcaemia is well associated with metastatic malignancy. Hypocalcaemia is an uncommon complication of osteoblastic metastases and occurs most commonly with breast and prostate carcinoma.
Case
A 46-year-old woman with metastatic breast carcinoma and osteoblastic skeletal metastases treated with denosumab presented with severe symptomatic hypocalcaemia. Serum calcium was persistently low with a nadir value of 1.45 mmol/l (2.2–2.6) and predated the use of denosumab. 25OH-cholecalciferol level was low (24.1 nmol/l). Serum PTH was inappropriately normal at 4.3 (1.3–7.3) for the prevailing level of hypocalcaemia suggesting hypoparathyroidism. Renal function and magnesium were normal.
Management
Treatment with intravenous calcium gluconate was instituted during symptomatic episodes. Vitamin D deficiency was managed with high dose choleclaciferol (20 000 IU, three times a week for 12 weeks) and oral calcium equivalent to 6 g of elemental calcium was commenced. Symptomatic hypocalcaemia persisted despite progressively increasing doses of elemental calcium (final dose 9 g). In view of persistent hypocalcaemia, treatment with Bendroflumethiazide 2.5 mg/day and Alfacalcidol 1 μg/day was instituted. The dose of Alfacalcidol was incrementally increased to 8 μg/day. Normocalcaemia was achieved in 16 weeks.
Discussion
Hypocalcaemia is an uncommon complication of malignancy and is caused by osteoblastic bone metastases. The putative mechanism is increased uptake of calcium by osteoblastic lesions. Hypocalcaemia in our patient was exacerbated by denosumab therapy and vitamin D deficiency. However, hypoparathyroidism in the context of severe hypocalcaemia was suggestive of impaired parathyroid reserve presumed secondary to microscopic malignant infiltration of the parathyroid glands.
Conclusion
Malignancy-related hypocalcaemia occurs almost exclusively with osteoblastic bone metastases and is generally associated with secondary hyperparathyroidism. Our case highlights the fact that microscopic malignant infiltration of the parathyroid glands can occur with advanced malignancy and result in severe refractory hypocalcaemia. Supraphysiological doses of elemental calcium and vitamin D are generally required to induce and maintain normocalcaemia.

DOI: 10.1530/endoabs.37.EP265

EP266

Osteoporotic fracture risk in menopausal women with obesity

Snjezana Popovic-Pejicic[1] & Vera Aksentic[2]
[1]Medical Faculty, Clinical Center Banja Luka, University Hospital, University of Banja Luka, Banja Luka, Republic of Srpska, Bosnia and Herzegovina; [2]Institute for Physical Theraphy and Rehabilitation, Banja Luka, Republic of Srpska, Bosnia and Herzegovina.

Introduction
Osteoporosis is a metabolic disease that is characterised by low mineral bone density (BMD) and increased risk of fractures. Weight loss reduced BMD and increased risk of hip fractures, while it reduces in a weight gain. Osteoporosis

fracture risk and BMI correlate more frequently denied in recent studies. The aim of this study was to examine relationship between BMI and BMD in a group of postmenopausal women.
Design
The study involved 100 postmenopusal women, aged 46 to 70 years (59.08 ± 6.07). BMD was determined by DXA method (dual energy X-ray absorptiometry) by Lunar Prodigy Advance Unit. BMD was measured at lumbal spine and both hips. BMI values were correlated with total *T* score values of the lumbal spine and both hips, as well as total *T* score values of spine and hip.
Results have shown that BMI was normal in 18% subjects, 1st grade obesity was found in 52%, 2nd grade obesity in 23%, 3rd grade obesity in 7% of subjects. Median BMI value was found in 28.27 ± 4.12. Median lumbal spine *T* score was −2.19 S.D. ± 1.25 , and hip *T* score −1.11 S.D ± 0.95. A statistically significant positive correlation was found between BMI and BMD of hip ($r=0.01$), whereas between BMI and BMD of lumbal spine there was no. There was, statistically significant correlation ($r=0.01$) between BMD values of lumbal spine and hip.
Conclusion
In postmenopausal women BMI is more important predictor of hip BMD, as compared to spine BMD. BMD of hip is increased with increase of BMI in postmenopausal women, what indicates that incidence of fracture of the hip decrease in women with obesity. A lack of correlation between BMI and BMD of spine might be due to predominant effect of lack of oestrogen and faster bone metabolism in spinal region.

DOI: 10.1530/endoabs.37.EP266

EP267

Evaluation of the effect of bisphosphonate therapy of postmenopausal osteoporosis using Dolga index

Jovanka Novakovic-Paro[1], Tijana Icin[1], Dragana Tomic-Naglic[1], Milena Mitrovic[1], Radoslav Pejin[1], Milan Dolga[3], Ivana Bajkin[1], Bojan Vukovic[2], Damir Benc[1], Djordje Popovic[1], Andrijana Milankov[1], Milica Medić-Stojanoska[1] & Branka Kovačev-Zavisic[1]
[1]Medical Faculty, Clinic of Endocrinology, Diabetes and Metabolic Diseases, Clinical Centre of Vojvodina, University of Novi Sad, Novi Sad, Serbia; [2]Medical Faculty, Emergency Center, Clinical Centre of Vojvodina, University of Novi Sad, Novi Sad, Serbia; [3]Smart Line Agency, Novi Sad, Serbia.

Introduction
Bisphosphonates are commonly used in the treatment of osteoporosis. The aim was to determine the effect of bisphosphonate therapy for osteoporosis on bone mineral density (BMD) depending on the Dolga index.
Materials and methods
The study included 36 postmenopausal women with osteoporosis. BMD was measured by DXA of the spine and hip before treatment and 2 years after starting bisphosphonate therapy. Parameters of bone turnover: osteocalcin and beta crosslaps were measured before treatment. On the basis of these values was calculated Dolga index. The Dolga index expresses excessive suppression of bone resorption and excessive suppression of the entire remodelling if the value obtained above 0.
Results
Average age of the respondents was 62.94 ± 8.49 years, with a mean BMI 25.60 ± 3.68 kg/m^2. After 2 years of therapy, a statistically significant difference in the parameters of bone remodelling and BMD (OC: 37.05 ± 14.36 vs 17.95 ± 5.62 ng/ml, $P<0.05$; beta crosslaps: 658.37 ± 264.57 vs 173.0 ± 96.92 pg/ml, $P<0.05$; L1–4 BMD: 0.813 ± 0.010 vs 0.862 ± 0.132 g/cm^2, total hip: 0.793 ± 0.08 vs 0.826 ± 0 07 g/cm^2; hip neck: 0.764 ± 0.08 vs 0.07 ± 0.788 g/cm^2. Using Dolga index, statistically significant improvement in spine and hip BMD were obtained in the group that did not have excessive suppression of bone resorption and bone remodelling. (L1–4: 0.803 ± 0.007 vs 0.842 ± 0.009 g/cm^2, $P<0.05$; total hip: 0.792 ± 0.007 vs 0.825 ± 0.008 g/m^2, $P<0.05$; hip neck: 0.780 ± 0.005 vs 0.802 ± 0.006 g/cm^2, $P<0.05$).
Conclusions
The use of bisphosphonate therapy leads to improvements in BMD with primary effect on bone resorption affecting the overall bone remodelling. The test results demonstrate the usefulness of the application of Dolga index in choosing patients with postmenopausal osteoporosis for the application of bisphosphonate therapy in order to achieve the best therapeutic effect. Continued research is ongoing on a larger sample in order to confirm the results, make new conclusions and recommendations for the treatment of postmenopausal osteoporosis bisphosphonate therapy.

DOI: 10.1530/endoabs.37.EP267

EP268

Patients with new onset diabetes after liver transplantation have higher sclerostin levels that tend to decrease after an oral glucose tolerance test

Guillermo Martínez Díaz-Guerra[1], Gonzalo Allo Miguel[1], Mercedes Aramendi Ramos[2], Soledad Librizzi[1], Sonsoles Guadalix Iglesias[1], Elena García Fernández[1] & Federico Hawkins Carranza[1]
[1]Endocrinology Service, 12 de Octubre University Hospital, Madrid, Spain; [2]Laboratory Service, 12 de Octubre University Hospital, Madrid, Spain.

Introduction
Decreased bone formation has been proposed as a mechanism involved in the higher risk of fractures in diabetic patients. Some clinical studies have found that sclerostin (SCL, a negative regulator of bone formation) is increased in diabetic patients. However, there is no information about the relationship between SCL and new onset diabetes after transplantation (NODAT). The aim of our study is to evaluate serum SCL levels in a cohort of patients with liver transplantation (LT).
Patients and methods
85 LT patients without previous diabetes mellitus were enrolled. A 75 g oral glucose tolerance test was performed (OGTT) and diagnostic ADA criteria were followed. Serum SCL was measured in fasting, 60- and 120-min samples during OGTT. MANOVA test were used to evaluate the evolution of sclerostin levels (from baseline to 120-min).
Results
48 patients (64%) showed normal glucose tolerance (NGT), 31 (36.4%) impaired glucose tolerance (IGT) and six NODAT (7.05%). Results of SCL for OTTG were (ng/ml; baseline, 60′, 120′): i) NGT: 0.70 ± 0.27/0.65 ± 0.22/0.69 ± 0.23 ng/ml; ii) IGT: 0.83 ± 0.31/0.71 ± 0.20/0.75 ± 0.20 ng/ml; iii) NODAT: 1.75 ± 1.20/1.55 ± 1.24/1.46 ± 1.1 ng/ml. SCL levels were significantly higher in NODAT patients at baseline ($P<0.001$); 60′ ($P<0.001$) and 120′ ($P=0.001$). During OGTT, sclerostin showed a significant decrease ($P=0.01$), which was more pronounced in the NODAT group, with a percent of change of: −0.32 ± 0.64.
Conclusions
Our results show that after LT basal SCL levels are higher in patients with NODAT than in patients with prediabetes or NGT. Also, we have found that during an OGTT sclerostin significantly decrease, particularly in NODAT patients. Based on our results, we suggest further studies to investigate a plausible link between higher levels of sclerostin in NODAT patients and their increased fracture risk.

DOI: 10.1530/endoabs.37.EP268

EP269

X-linked hypoparathyroidism: an Indian kindred!

Ravindra Shukla, Asish Basu & Animesh Maity
Medical College Kolkata, Kolkata, West Bengal, India.

Introduction
X-linked hypoparathyroidism is an extremely rare disease, so far described in only two multigenerational kindreds. In US, who later on the genetic testing were found to be interrelated. W describe X-linked congenital hypoparathyroidism in a family from India.
Case report
Case 1 presented with hypocalcaemic non-febrile generalised tonic clonic seizures at 16 months of age. Seizures controlled after hypocalcaemia correction. He was put on T. calcitriol 0.5 mg B.D, 1.5 g calcium/day. Case 2 presented with hypocalcaemic neonatal generalised tonic clonic seizure. He was put on calcitriol 0.5 mg/day, 1 g of calcium. Both had delayed milestones and growth, developed

Table 1

Case	S.calcium at diagnosis (mg/dl)	S.phosphorus at diagnosis (mmol/l)	Vit. D at diagnosis	iPTH at diagnosis	S.calcium at present (mEq/l)	S.phosphorus at present (mEq/l)	iPTH at present	Average 24 hr urinary calcium in last 6 years
19-year male	1.05	10.61	16	<1	8.4	6.1	5.2	340
14-year male	2.3	9.4	12	<1	9	5.3	3.9	290
19-year old sister	9.6	4						
22-year old sister	9.4	4.3						
Father	9.8	3.9						
Mother	8.6	4.8						

B/L cataract and B/L basal ganglia calcification, required addition of phenobabitone at 10–12 year of age. Parents and two sisters are asymptomatic. History of death of a male child at age of 2 years on maternal sides (Table 1).
Conclusion
This is first report of X-linked hypoparathyroidism outside the Missouri kindred. The two brothers exibit strikingly similar phenotype. In addition we also describe abnormalities of dentition and cataract in presence of seemingly adequate calcitriol and calcium replacement. Genetic analysis of such family could throw insight into as yet known aspects of parathyroid gland development and disease.

DOI: 10.1530/endoabs.37.EP269

EP270

A case of a mitochondrial myopathy with multiple endocrinopathy

Mina Gulfem Kaya[1], Sefika Burcak Polat[1], Sebnem Eker Guvenc[2], Sahin Doganay[3], Reyhan Ersoy[3] & Bekir Cakir[3]
[1]Department of Endocrinology and Metabolism, Atatürk Education and Research Hospital, Ankara, Turkey; [2]Department of Family Medicine, Atatürk Education and Research Hospital, Ankara, Turkey; [3]Department of Endocrinology and Metabolism, Faculty of Medicine, Yildirim Beyazit University, Ankara, Turkey.

Introduction
Mitochondrial diseases usually occur by mutations of mitochondrial or nuclear DNA. Mitochondrial cytopathy is a disease affecting many systems including endocrine system. We present a case diagnosed as mitochondrial myopathy previously accompanying multiple endocrinological pathologies.
Case
Fifty-two years old female patient admitted in another center with a complaint of drooping of upper eyelids 25 years ago. Acetylcholine receptor antibodies were negative and her EMG was compatible with progressive external ophthalmoplegia. She was diagnosed as mitochondrial myopathy by left biceps muscle biopsy. Coenzym Q 10 and L-carnitine treatments were started. She admitted to our center with numbness and spasm in her hands. Serum calcium was 6.1 mg/dl, phoshorus was 6.9 mg/dl, magnesium was 1.5 mg/dl and parathyroid hormone level was 8.9 pg/ml. There were common symmetric calcifications at basal ganglions, bilateral cerebellar hemispheres, thalamus and periventricular white matter in cranial CT. EEG was normal. Creatine kinase was 507 U/l, LDH was 435 U/l and plasma lactate level was 2.4 mmol/l. Calcium carbonate and calcitriol were administered to the patient with diagnosis of hypoparathyroidism. Thyroid autoantibodies were positive. Thyroid hormone levels were normal. Thyroid ultrasound was compatible with chronic thyroiditis. In eye examination bilateral ptosis and cataract were detected. Retina examination was normal. Her audiometry was normal. She was diagnosed as type 2 DM.
Conclusion
Mitochondrial myopathies can be together with various endocrinological problems. Our patient had adult onset pure mitochondrial cytopathy and primary hypoparathyroidism, chronic autoimmune thyroiditis and type 2 DM were accompying endocrinological pathologies. Associations with hypoparathyroidism, autoimmune thyroiditis, DM and GH deficiency have been reported in patients with Kearns Sayre syndrome in the literature. Also mitochondrial myopathy, encephalopathy, lactic acidosis, stroke (MELAS) and adrenal insufficiency's association was reported. Because of probability of affecting multisystem, cases with mitochondrial myopathies should be evaluated for various endocrinological pathologies.

DOI: 10.1530/endoabs.37.EP270

EP271

Vitamin D receptor genotypes and their association with the 5-year changes in bone mineral density in Spanish postmenopausal women

Jose M Moran, Maria Pedrera-Canal, Jesus M Lavado-Garcia, Raul Roncero-Martin, Purificacion Rey-Sanchez, Julian F Calderon-Garcia & Juan D Pedrera-Zamorano
Metabolic Bone Diseases Research Group, University of Extremadura, Caceres, Spain.

Our aims were to follow the longitudinal changes after 5-year in femoral neck (FN), femoral trochanter (FT), L2, L3, L4 and L2–L4 bone mineral density (BMD) in Spanish postmenopausal women and to study whether the polymorphism BsmI in the vitamin D receptor (VDR) may influence these results. We conducted a 5-year prospective study of BMD and its change in 174 women, aged 43–78 years. BMD was measured by densitometry. The women were members of the Caceres Reference Database for the Diagnosis of Osteoporosis (CAFOR), a population-based longitudinal study of BMD. Changes were analysed by Wilcoxon test. We also examined the effect of adjustments for dietary and anthropometric factors on these associations. After the 5-year period significant changes were observed in L3, L4, L2–L4, FN and FT ($P<0.001$ in all cases). No significant changes were observed in L2 ($P=0.598$). Before adjustments, in women homozygous for the b allele (genotype (bb) $n=25$) no significant changes were observed ($P>0.05$ in all cases). Women heterozygous (genotype (Bb) $n=73$) had less FT BMD ($P<0.001$), L4 ($P<0.001$) and L2–L4 ($P=0.010$) over time; no changes were observed over the 5-year period in Bb women in FN, L2 and L3 BMD. In women homozygous for the B allele ($n=76$) significant loss in BMD was observed in FN ($P=0.010$) and FT ($P<0.001$) BMD as well as in L4 ($P<0.001$) and L2–L4 ($P=0.012$) BMD after the 5-year period. No changes were observed in L2 and L3 BMD ($P>0.05$ in both cases). Upon adjustment for dietary and anthropometric factors no further statistically significant associations to BsmI polymorphism were found.
Our results reveal that to correctly address the association between bone loss and VDR polymorphism BsmI in small samples, it is necessary to consider the variations in dietary and anthropometric factors.

DOI: 10.1530/endoabs.37.EP271

EP272

Cinacalcet remains effective in primary hyperparathyroidism after 4 years of treatment

Inés Luque-Fernández, Florentino Del Vall, Alessandra Luque, Almudena Vicente, Julia Sastre & Amparo Marco
Hospital Virgen de la Salud, Toledo, Spain.

Introduction
Cinacalcet is an oral calcimimetic indicated in treatment of primary hyperparathyroidism in patients who are unable to undergo parathyroidectomy: do not accept surgery, there is failure of previous surgery or serious comorbidity that makes surgery impossible.
Methods
Descriptive study that includes nine patients with primary hyperparathyroidism who have completed at least 48 months of treatment with cinacalcet (seven patients refusal to parathyroidectomy and two surgery not possible due to comorbidities). We recorded clinical and biochemical data at baseline and after 3, 6, 12, 24 and 48 months of treatment.
Results
Median time of treatment was 49 months. After 12 months serum calcium was significantly decreased as compared to baseline (10.12 vs 11.59 mg/dl $P=0.008$) and phosphorus levels were significantly increased (2.84 vs 2.45 mg/dl $P=0.021$). No significant differences were observed in PTH levels (155.45 vs 136.9 pg/ml $P=0.6$). No further variation was observed after 24 and 48 months compared to 12 months follow up except for an increase in PTH to baseline levels. As compared to baseline, after 4 years of therapy, serum calcium remained significantly decreased (10.13 vs 11.59 mg/dl $P=0.008$) and serum phosphorus significantly increased (2.93 vs 2.45 mg/dl $P=0.02$). Normocalcemia (S-Ca <10.2 mg/dl) was achieved in 55.7% of patients. Usually the medication was well-tolerated and no serious adverse events were observed.
Conclusion
Hypercalcemia is rapidly improved by Cinacalcet and remains stable after 48 months follow-up. Cinacalcet is an effective and safe alternative in non-surgical treatment of primary hyperparathyroidism.

DOI: 10.1530/endoabs.37.EP272

EP273

Bone mineral density evolution after parathyroidectomy in patients with primary hyperparathyroidism

Alicia Vicuña, Ana Ramos-Leví, Miguel Sampedro-Nuñez, Sandra Campos, Magaly Zelada & Mónica Marazuela
Department of Endocrinology and Nutrition, Hospital Universitario de la Princesa, Madrid, Spain.

Introduction
Primary hyperparathyroidism results in increased bone resorption. The presence of osteoporosis is at present an established surgery criteria.

Objective
The aim of this study was to evaluate the changes in bone mineral density (BMD) after surgery in patients with primary hyperparathyroidism.
Material and methods
Retrospective study of 58 patients with primary hyperparathyroidism treated by parathyroidectomy from 2004 to 2012. We analysed the percent change in BMD of spine, hip and radio densitometry 12 and 36 months after surgery.
Results
Among the 58 patients enrolled, we obtained densitometry data of 26 patients after 12 months and 37 after 36 months. The average age of the patients was 61 ± 12 years and 70.7% were women. We observed an increased BMD at lumbar spine and hip 1 year after surgery (+2.3% ± 5.1, $P=0.027$; +5.7% ± 6.3, $P=0.000$, respectively). Improvement at 36 months was also observed in both locations (+4.9% ± 7.4, $P=0.001$; +8.5% ± 6.0, $P=0.000$). In radio, there were no changes in BMD in any of the follow-up times, although a slight increase at 36 months (+0.96% ± 4.2, $P=0.576$) was observed. Sixteen of the 58 patients (27.6%) also were treated with bisphosphonates. There were no differences in changes of BMD between these patients and those who did not received bisphosphonates.
Conclusion
Hip and spine BMD improved 1 and 2 years after surgery in patient's whit primary hyperparathyroidism. It would be interesting to evaluate the response to longer term.

DOI: 10.1530/endoabs.37.EP273

EP274

Effect of the inhibition of a cholesterol membrane transporter on vitamin D absorption: a double-blind randomised placebo-controlled study

Mariana Costa Silva[1], Gustavo A M Faulhauber[1,2], Érica N Leite[2], Kamila R Goulart[2], Jorge M A Ramirez[2], Fernanda M Cocolichio[2] & Tania W Furlanetto[1,2]
[1]Postgraduation Program in Medicine: Medical Sciences, Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil; [2]Internal Medicine Division, Hospital de Clinicas de Porto Alegre, Porto Alegre, RS, Brazil.

Introduction
Oral supplements are important to prevent and treat vitamin D deficiency. Membrane transporters could be involved in its absorption. As vitamin D is structurally similar to cholesterol, it is possible that they share absorption mechanisms. Ezetimibe decreases cholesterol absorption, through inhibition of NPC1L1 transporter. It has been shown *in vitro* and in rodents that ezetimibe decreases vitamin D absorption, so the aim of this study was to evaluate the effect of ezetimibe on 25-hydroxyvitamin D [25(OH)D] levels in response to a single oral dose of vitamin D, in young persons.
Methods
This randomised, double-blind, placebo-controlled trial (ClinicalTrials.gov NCT02234544) was developed in a South Brazilian University Hospital. Fifty-one medical students were randomised to ezetimibe 10 mg/day or placebo for 5 days. On the 5th and 19th days, blood samples for 25(OH)D, PTH, calcium, and albumin were collected after overnight fast. On the 5th day, all participants received a single oral 50 000 IU cholecalciferol dose during a 15 g fat meal. 25(OH)D was measured by the immunoassay Diasorin Liaison. Measurements were compared in a general linear model adjusted for multiple comparisons by the Bonferroni test.
Results
At baseline, 25(OH)D was <30 and <20 ng/ml, respectively, in all and 82.3% of the participants. Fourteen days after a single 50 000 IU oral dose of cholecalciferol, the mean (S.D.) change in 25(OH)D was of 8.75 (3.74) ng/ml in the ezetimibe group, vs 10.02 (3.84) ng/ml in the placebo group, after adjustment to baseline 25(OH)D levels and BMI ($P=0.26$). Mean 25(OH)D, PTH, calcium and albumin remained similar in both groups.
Conclusions
Ezetimibe had no effect on the mean change in serum 25(OH)D after a single oral dose of cholecalciferol.
Disclosure
University hospital research incentive fund (FIPE/HCPA project 14-0378).

DOI: 10.1530/endoabs.37.EP274

EP275

Acquired FGF23 resistance: the primacy of parathyroid hormone over fibroblast growth factor 23 in renal phosphorus handling

Malachi McKenna[1,2], Sinead Kinsella[1], Michelle Morrin[1], Melissa Sloman[3], Ahad Abdalla[1], Myra O'Keane[1], Barbara Murray[1], John Holian[1,2], Alan Watson[1,2] & Mark Kilbane[1]
[1]St Vincent's University Hospital, Dublin, Ireland; [2]University College Dublin, Dublin, Ireland; [3]Royal Devon and Exeter NHS Foundation Trust, Exeter, UK.

Introduction
Fibroblast growth factor 23 (FGF23) excess is the cause of chronic hypophosphatemia in rare conditions such as X-linked hypophosphataemic rickets (XLHR) and tumour-induced osteomalacia (TIO), but animal studies indicate that the effect of FGF23 on serum phosphorus is dependent on the presence of parathyroid hormone (PTH). In this case series of rare disorders with abnormalities in renal phosphorus handling, we sought to explore the relative roles of PTH and FGF23 on renal handling of phosphorus.
Methods
We studied 16 patients with congenital hypophosphatemia (of whom two were hypoparathyroid post total parathyroidectomy), two patients with TIO, one patient with hypophosphataemic bone disease due to congenital renal tubular acidosis, and three patients with hypoparathyroidism (HP). We performed genetic mutation analysis, and we measured FGF23, PTH, renal phosphorus threshold (TmP/GFR), ionised calcium, 25-hydroxyvitamin D (25OHD), and a panel of bone turnover markers (BTMs). We also studied 30 patients with chronic kidney disease (CKD) who had estimated glomerular filtration (eGFR) stages 3–5.
Results
Patients with congenital hypophosphatemia and TIO had low TmP/GFR and varying degrees of FGF23 excess. The patient with hypophosphatemia and renal tubular acidosis had the lowest FGF23 and the three patients with HP had low PTH, elevated FGF23, but high TmP/GFR. The two patients with congenital hypophosphatemia and hypoparathyroidism had normal TmP/GFR despite having marked elevation in both C-terminal and intact FGF23. Both patients had CKD, but FGF23 was still about tenfold higher than expected for level of eGFR.
Conclusions
While FGF23 is a determinant of TmP/GFR in congenital and acquired disorders of dysregulated FGF23 production, the full effect of FGF23 on TmP/GFR is dependent on PTH secretion. FGF23 resistance is extant when PTH is absent.

DOI: 10.1530/endoabs.37.EP275

EP276

Lower levels of vitamin D as a predictor of reduced muscle strength in moderately obese postmenopausal women

Miljanka Vuksanovic[1], Branka Arsenovic[1], Milica Marjanovic Petkovic[2], Andjela Gavrilovic[3] & Teodora Beljic Zivkovic[1,4]
[1]Division of Endocrinology, Diabetes and Metabolism, Section of Osteoporosis and Bone Densitometry, Zvezdara University Hospital, Belgrade, Serbia; [2]Division of Endocrinology, Diabetes and Metabolism, Zvezdara University Hospital, Belgrade, Serbia; [3]Division of Neurology, Zvezdara University Hospital, Belgrade, Serbia; [4]Belgrade University School of Medicine, Belgrade, Serbia.

Introduction
Low concentration of serum 25-hydroxyvitamin D (25-OHvitD) have been associated with low bone loss and risk of falls in postmenopausal women. Moderate obesity is not a risk factor for osteoporosis.
Aim
The aim of this study was to investigate how vitamin D concentration correlates with muscle strength and bone density in moderately obese postmenopausal women.
Methods
We include 33 postmenopausal women, between 50 and 60 years of age, coming for the first measure of dual-energy X-ray absorptiometry (DXA). The assessed parameters were: BMI, waist circumference (WC), 25-OHvitD, bone mineral density (BMD) measured by DXA and muscle strength. Muscle strength was measured as hand grip strength (HGS) with JAMAR Hand Dynamometer. Three measures on the right or left hand were averaged to get the absolute HGS and compared to the normative data for this aged group (47.3–57.3 pounds). *T*-test for

continuous variables and Spearman test for correlations between variables were used.
Results
The postmenopausal women were 56.4±2.8 years old, menopausal duration 6.5±2.7 years, with BMI 28.01±3.4 kg/m^2 and WC 89.0±8.1 cm. The mean level of 25-OHvitD was 32.5±13.9 nmol/l. A significant negative correlation was observed between 25-OHvitD levels and both WC ($\rho_{wc}=-0.65$; $P<0.001$) and BMI ($\rho_{bmi}=-0.49$; $P<0.003$). The average HGS of these moderately obese participants was 28.3±4.2 pounds. It was significantly lower than the normative grip strength for referent range group ($t=-21.65$; $P<0.001$). A significant positive correlation was observed between 25-OHvitD levels and HGS ($\rho_{hgs}=0.45$; $P<0.009$). Average BMD on lumbar spine was 0.862 and 0.668 g/cm^2 on total hip. There was a very weak correlation between serum 25-OHvitD and BMD at lumbar spine ($\rho=0.167$; $P=0.35$) and hip ($\rho=0.228$; $P=0.20$).
Conclusion
Decreased levels of 25-OHvitD in moderately obese postmenopausal women are associated with low muscular strength. Decreased muscular strength may increase the risk of falls and fracture in moderately obese postmenopausal women.

DOI: 10.1530/endoabs.37.EP276

EP277

Evaluation of calcium and vitamin D disorders: case report of two patients

Andreja Maric
County Hospital Cakovec, Cakovec, Croatia.

Introduction
Differential diagnosis of hypocalcaemia is extensive, and careful diagnostic algorithm should be performed to adequately treat hypocalcaemic disorders.
Case report
Two female patients with hypocalcaemia are presented. The first one was 49 years old, admitted to hospital due to weakness, hampered mobility and bone pain (hips, thorax). Six years ago she was hospitalized due to chronic renal failure, osteoporosis, fractures of hip neck and both pubic bones, but did not take any medication. Current diagnostic procedures revealed several rib fractures (X-ray), and laboratory tests showed: iron deficiency, urea and creatinine increased, high alkaline phosphatase (297 U/l), low total serum (1.8 mmol/l) and ionizing calcium (0.56 mmol/l), low urinary calcium, low serum phosphate, low vitamin D (34 nmol/l) and vitamin B12 values, and high PTH (44.3 pmol/l) and bone markers. Densitometry (DXA) showed characteristics for severe osteoporosis. The diagnosis of osteomalacia was made, and therapy with calcitriol (2× 0.25 μg/day), calcium ($CaCO_3$ 3×1 g), vitamin B12 and folate was introduced, with significant clinical improvement. Other patient was 39 years old, admitted due to chronic bone pain and suspected bone metastases on scintigraphy. Medical history revealed cerebral palsy, epilepsy and chronic gastritis. Diagnostic evaluation did not confirmed malignant disease, but hypocalcemia (1.97 mmol/l) and hypophosphatemia (0.46 mmol/l) were found. TSH (7.72 mIU/l) and PTH (21.3 pmol/l) were increased, with low vitamin D (9.3 nmol/l) and high alkaline phosphatase (360 U/l). DXA showed low bone mineral density. Final discharge diagnosis were osteomalacia, hypothyroidism and megaloblastic anemia. Calcium ($CaCO_3$ 1 g) and vitamin D replacement therapy (4000–6000 drops/day) were started, with clinical and laboratory tests improvement.
Conclusion
Calcium, PTH and vitamin D disorders require detailed medical history, diagnostic evaluation and differential diagnosis. Adequate therapy, monitoring and follow up guarantee well treated and satisfied patient.

DOI: 10.1530/endoabs.37.EP277

EP278

25-OH vitamin D: a predictor of clinical outcomes in primary hyperparathyroidism

Mustafa Sahin, Gozde Sengul Aycicek, Demet Corapcioglu, Rıfat Emral, Sevim Gullu, Murat Faik Erdogan, Vedia Tonyukuk Gedik, Nilgun Başkal & Ali Rıza Uysal
Ankara University, Ankara, Turkey.

Objectives
We aimed to find if there is any relationship between vitamin D levels and clinical, laboratory parameters and osteoporosis, in primary hyperparathyroidism (PHPT).
Material and methods
128 patients with PHPT and 30 patients as a control group were analysed. Patients with PHPT were grouped due to vitamin D levels and levels low than 20 μg/ml accepted as deficiency.
Results
Patients with 25-OH vitamin D <20 μg/l were younger ($P=0.043$). Also they were more obese; BMI ≥30 ($P=0.18$) and more hypertensive ($P=0.032$). Metabolic syndrome (MS) incidence was higher in the patients with 25-OH vitamin D levels <20 μg/l ($P=0.44$). Incidence of thyroid nodules and thyroid nodule volume were similar between two groups. Also, fasting plasma glucose (FBG), HDL, LDL, triglyceride (TG), creatinine (Cr), glomerular filtration rate (GFR), TSH, T_4, PTH, Ca, 24 h urinary Ca and neuthrophil/lymphocyte ratio were similar. There was no significant difference in the incidence of nephrolithiasis, osteoporosis and parathyroid adenoma size between the groups. MS incidence was higher (32.8%) in PHPT ($P=0.042$). 25-OH vitamin D was found to be associated with age, BMI, thyroid volume and triglyceride in regression analyses.
Conclusion
25-OH vitamin D levels may be an indicator of hypertension (HT) and MS in PHPT. It also may be used as a treatment target in the severe disease.

DOI: 10.1530/endoabs.37.EP278

EP279

The diagnostic value of parathyroid hormone washout in primary hyperparathyroidism patients with negative or unequivocal 99mTc-MIBI results

Cevdet Aydin[1], Sefika Burcak Polat[1], Fatma Dilek Dellal[1], Cafer Kaya[1], Seyda Turkolmez[2], Mehmet Kilic[3], Reyhan Ersoy[1] & Bekir Cakir[1]
[1]Endocrinology and Metabolism Department, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey; [2]Nuclear Medicine Department, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey; [3]General Surgery Department, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey.

Introduction
Primary hyperparathyroidism (pHPT) is a common endocrine disease mainly caused by single or multiple hyperfunctioning parathyroid lesions. In 2–7% of cases, surgery is not curative at first operation and reoperation is required. Ultrasonography and sestamibi scan are the most widely used methods for identification of the culprit parathyroid gland with the disadvantage of high false positives caused by other cervical pathologies. Herein we aimed to search the diagnostic value of measurement of parathyroid hormone (PTH) concentration in the needle washout of suspicious lesions suggestive for parathyroid adenoma with negative or unequivocal MIBI results.
Methods
Our endocrine database was searched retrospectively for the patients with PHPT who underwent PTH washout. There were 100 lesions of 70 patients. Among them, 21 lesions in 16 patients were operated and data of these lesions were analysed. All patients had at least one suspicious parathyroid lesion detected by ultrasonography and all patients were evaluated by 99mTc-MIBI.
Result
The mean age of the patients was 53.3±10.6 years with the majority of them being female (87.5%). The mean preoperative serum calcium level was 11.04± 0.33 mg/dl. The median serum PTH level was 140 pg/ml (ranging from 55 to 371) and the median serum PTH washout level was 3316 pg/ml ranging from 13 to 5000. Preoperatively 99mTc-MIBI scan was negative or unequivocal in 15 of 21 operated lesions while it was positive in six. For the lesions that the MIBI failed to localise, the sensitivity of PTH washout was 91% and the specificity was 66%.
Conclusion
PTH washouts can contribute significantly in establishing the parathyroid nature of cervical lesions that has conflicting preoperative sestamibi results and also might help the surgeon to perform a more successful operation.

DOI: 10.1530/endoabs.37.EP279

EP280

Proximal femur strength, cortical thickness and bone structure in Klinefelter syndrome

Enrico Schileo[2], Alberto Ferlin[1], Ilaria Palmadori[2], Fulvia Taddei[2], Alessandro Coran[1], Sigurdur Sigurdsson[3], Vilmundur Gudnason[3], Tamara Harris[4] & Carlo Foresta[1]
[1]Department of Medicine, University of Padova, Padova, Italy; [2]Istituto Ortopedico Rizzoli, Bologna, Italy; [3]Icelandic Heart Association, Kópavogur, Iceland; [4]National Institute on Aging, Bethesda, Maryland, USA.

Introduction
Klinefelter syndrome patients (KS) frequently show low bone mass, which could have multiple aetiologies. The structural basis of low bone mass and its consequences on bone strength are almost not known, but analogies in bone microstructure and strength between KS and ageing women have proposed by studying distal tibia by HRpQCT. The aim of this study was to compare proximal femur strength and bone structure of KS with elderly women and men.
Patients and methods
Proximal femur QCT analysis was performed on 18 KS (mean age 44 ± 8 years) and compared with 89 elderly women (76 ± 6 years) and 39 elderly men (79 ± 5 years). QCT-based estimates of proximal femur strength were obtained with a personalized Finite Element procedure previously validated *in-vitro* and *in-vivo* under loading conditions corresponding to ten fall directions to span accidental conditions. Bone structure analysis included trabecular and cortical volumetric bone mineral density (Tb.vBMD, Ct.vBMD), and cortical thickness (Ct.Th.), mapped to 18 sectors covering the whole femoral neck. Femoral neck length and cross-sectional area were calculated.
Results
KS and women had similar bone strength (KS: 2981 ± 514 N, W: 2822 ± 627 N, Mann–Whitney $P = 0.14$), both significantly lower ($P < 0.001$) than elderly men (4176 ± 985 N). Bone cortex was significantly thinner in KS patients with respect to women ($P < 0.05$ in 13 out of 18 sectors). Ct.vBMD was equivalent in KS and women, whereas Tb.vBMD was instead higher in KS ($P = 0.003$). Femoral neck was significantly larger in KS patients (CSA 25% higher, $P < 0.001$).
Conclusion
We showed for the first time that, at proximal femur, KS and elderly women are similar in terms of bone strength. This similarity emerged however from different structural traits: KS had thinner femoral neck cortex, partially compensated by a denser trabecular compartment and larger bone dimensions (i.e. higher moments of area and bone mass).

DOI: 10.1530/endoabs.37.EP280

EP281

^{18}F-fluorocholine as PET tracer to localize the dominant source of PTH in a patient with X-linked hypophosphataemia and hyperparathyroidism

Christoph Schmid[1], Andrea Babians-Brunner[1], Gerry Huber[2], Bertram Sah[3] & Hans Steinert[3]
[1]Endocrinology and Diabetology, Zürich, Switzerland; [2]Otorhinolaryngology, Zürich, Switzerland; [3]Nuclear Medicine, Zürich, Switzerland.

Introduction
^{18}F-fluorocholine is a PET tracer used in the diagnostic work-up of patients with prostate cancer but was incidentally found to detect other tumours such as meningiomas, pituitary and parathyroid adenomas. ^{18}F-fluorocholine PET/MRI is currently under investigation as an imaging tool for detecting hyperfunctioning parathyroid glands in primary or secondary hyperparathyroidism, especially in patients qualifying and willing to undergo parathyroid surgery where standard diagnostic localization procedures such as neck ultrasound and scintigraphy failed to localize an adenoma.
Case report
A male patient was diagnosed with X-linked hypophosphataemic rickets at the age of 5 years with severe dwarfism and leg deformities. Treated with phosphate supplements and calcitriol (and several orthopaedic correction surgeries), he reached reasonable growth and height, with at least partial correction of mineralization deficit and without obvious kidney damage. As expected, tubular phosphate reabsorption (TmP/GFR) remained low (< 0.4 mmol/l) and FGF23 remained high. At the age of 23 years, he developed hypercalcaemia which persisted after treatment (including calcitriol) was stopped, i.e. a laboratory constellation of primary hyperparathyroidism. However, both neck ultrasound and dual-isotope ^{99m}Tc-tetrofosmin and ^{123}I sodium iodide SPECT failed to localize an adenoma. Since the patient and his physicians preferred surgery (rather than cinacalcet) when feasible with maintaining normal parathyroid function, the patient consented to off-label imaging with ^{18}F-fluorocholine PET/MRI, revealing intense focal tracer accumulation at the right lower position. Minimally invasive videoassisted selective parathyroidectomy was performed, resulting in an intraoperative drop of PTH from 258 to 73 ng/ml and subsequent normalization of serum calcium. Calcium and PTH remain normal for more than a year of follow-up, up to this writing.
Conclusion
Our finding suggests that ^{18}F-fluorocholine PET/MR can be a helpful and sensitive tool to localize the dominant source of PTH in difficult selected cases where minimally invasive selective parathyroidectomy is considered the treatment of choice.

DOI: 10.1530/endoabs.37.EP281

EP282

A prospective study on juvenile primary hyperprathyroidism population

Federica Saponaro, Federica Cacciatore, Edda Vignali, Antonella Picone, Chiara Banti, Antonella Meola, Simona Borsari, Elena Pardi, Claudio Marcocci & Filomena Cetani
Endocrinology U.O., University of Pisa, Pisa, Italy.

Primary hyperparathyroidism (PHPT) is a common disorder in adults but is uncommon in young people and features of juvenile PHPT (J-PHPT) are debated in literature. The aim of the study was to evaluate the characteristics of PHPT in juvenile sporadic (S) and familial (F) patients. It's a monocentric prospective study at a referral centre in 154 patients with ≤ 40 years. Patients were evaluated at diagnosis and at the last follow-up visit (median follow-up 2 years), comparing clinical presentation, biochemical, densitometric, histological parameters, percentage of cure after parathyroidectomy (PTx) between S and F. One hundred-twelve patients had SJ-PHPT, 31 patients had multiple endocrine neoplasia type 1 (MEN1) syndrome and 11 familiar isolated hyperparathyroidism (FIHP). Symptomatic nephrolithiasis was observed in 44% of SJ-PHPT and in 48.4% of FJ-PHPT and aspecific neuropsychic symptoms in 95% of all patients. Ninety SJ-PHPT and 27 FJ-PHPT underwent PTx. The histology showed in SJ-PHPT and FJ-PHPT respectively: a single adenoma in 86 and seven patients, hyperplasia in two and 19 patients, carcinoma in one SJ-PHPT and exploration without excision of parathyroid tissue was observed in one S-JPHPT and one F-JPHPT. Ionized serum calcium and PTH significantly decreased after PTx in both group. The persistence/recurrence rate of disease was 15% in sporadic cases and 52% in familial cases. There were not statistically significant ($P < 0.001$) differences in biochemical and densitometric markers between sporadic and familial group. In both groups males showed a more statistically significant ($P < 0.001$) severe PHPT for both biochemical and densitometric markers. When the overall patients were stratified for age ≤ 25 and > 25 years, younger patients appeared to have a significantly ($P < 0.001$) more severe disease.
In conclusion, J-PHPT is generally sintomatic and more severe in males; it has a higher rate of persistence/recurrence disease, even in sporadic patients; S and F patients show similar features.

DOI: 10.1530/endoabs.37.EP282

EP283

Outcome of subtotal parathyroidectomy in patients with renal hyperparathyroidism

Kiera Welman, Peter Veitch & Neal Banga
Royal Free London NHS Foundation Trust, London, UK.

Introduction
Hyperparathyroidism is common in patients with end-stage renal failure (ESRF): up to 20% require treatment for hyperparathyroidism within 10 years of commencing haemodialysis. Despite the significant cost of long-term medical treatment with calcimimetics and poor patient compliance, only a minority of patients are referred for surgery, usually due to their significant co-morbidity.
Methods
Outcome data of patients with secondary or tertiary hyperparathyroidism undergoing subtotal parathyroidectomy in our department from 2012 to 2014 were reviewed. All patients underwent bilateral neck exploration with nerve monitoring. Serum parathyroid hormone (PTH) and calcium levels were measured postoperatively.

Results
25 patients (median age 52 years) underwent subtotal parathyroidectomy. 18/25 patients (72%) had ESRF and secondary hyperparathyroidism whilst 7/25 patients (28%) had post-transplant tertiary hyperparathyroidism. The majority of patients had evidence of osteopaenia or osteoporosis on bone densitometry and 17/25 patients (68%) had some degree of hypercalcaemia at referral. At least four parathyroid glands were identified intra-operatively in 19/25 patients (76%) and a subtotal procedure was performed, leaving ~50 mg of parathyroid tissue in-situ. In 6/25 patients, three or fewer parathyroid glands were identified, and in these patients all the identified glands were excised. 24/25 patients (96%) had serum PTH levels <14 pmol/l at most recent follow up (range 3–24 months). Normocalcaemia was achieved in 16/17 (94%) of the patients who were hypercalcaemic pre-operatively. Post-operative complications included severe transient hypocalcaemia requiring i.v. calcium infusion in two patients, and one patient required emergency reoperation for bleeding. One patient experienced temporary unilateral recurrent laryngeal nerve palsy which recovered fully within 3 months post-surgery.
Conclusion
Subtotal parathyroidectomy can deliver biochemical success in >90% of patients with renal hyperparathyroidism. It offers a safe and cost-effective alternative to medical treatment, particularly in patients with poor compliance, and without the risk of future adynamic bone disease associated with total parathyroidectomy.

DOI: 10.1530/endoabs.37.EP283

EP284

Asymptomatic pulmonary cement embolism after vertebroplasty: a case report

Zoe A Efstathiadou, Eleni Karathanassi, Maria Poulasouchidou & Marina D Kita
Department of Endocrinology, 'Hippokration' General Hospital of Thessaloniki, Thessaloniki, Greece.

Introduction
Vertebroplasty is a commonly performed technique in the management of vertebral compression fractures. However, it is associated with some serious adverse effects. Most complications are related to the leakage of bone cement (polymethylmethacrylate) into the spinal canal or the perivertebral venous system.
Case report
A 74-year-old lady was subjected to percutaneous verterbroplasty for osteoporotic compression fractures on T11, T12, L1 and O4. The procedure was uneventful. One year later, on routine chest radiograph, a high density material was found in branches of pulmonary artery. The same material was also found in the perivertebral venous system and had identical density with the bone cement present in the treated vertrebrae. Findings were confirmed by chest computed tomography. No specific medical treatment was given.
Conclusion
Biologic cement leakage is a frequent adverse event of vertebroplasty, with pulmonary cement embolism occurring in about one-quarter of the patients and remaining in most cases asymptomatic. However, close monitoring and early recognition of this clinical situation might be critical for some patients.

DOI: 10.1530/endoabs.37.EP284

EP285

Low extracellular sodium promotes adipogenic commitment of human mesenchymal stromal cells: a novel mechanism for chronic hyponatremia-induced bone loss

Cristiana Deledda[1], Benedetta Fibbi[1], Corinna Giuliani[1], Susanna Benvenuti[1], Paola Luciani[1], Benedetta Mazzanti[2], Riccardo Saccardi[2] & Alessandro Peri[1]
[1]Department of Experimental and Clinical Biomedical Sciences 'Mario Serio', University of Florence, Firenze, Italy; [2]Department of Hematology, Careggi Hospital, Firenze, Italy.

Hyponatraemia represents an independent risk factor for osteoporosis and fractures, affecting both bone density and quality. A direct stimulation of osteoclastogenesis and bone resorption in the presence of reduced extracellular sodium concentrations ([Na+]) has been shown, but, to date, the effects of reduced [Na+] on osteoblasts have not been elucidated. This study investigated the effects of a chronic reduction of extracellular [Na+], independently of osmotic stress, on human mesenchymal stromal cells (hMSC) from bone marrow, the common progenitor for osteoblasts and adipocytes. As regards hMSC homeostasis, we found a significant inhibition of adhesion and viability, but no alteration of their surface antigen profile and immuno-modulatory properties. Low extracellular [Na+] were able to modulate the osteoblastic production of factors (MCP-1 and CXCL-12) that stimulate osteoclast recruitment and bone resorption. Next, we tested whether chronic hyponatremia was able to alter the cellular commitment of hMSC. We found that hMSC maintained their ability to commit toward the osteogenic and the adipogenic phenotypes, as demonstrated by the unaltered gene expression of specific differentiation markers. However, the dose-dependent increase in the number of adipocytes as a function of reduced [Na+], observed by Oil-Red-O staining, suggested a preferential commitment toward the adipogenic phenotype at the expense of osteogenesis. This observation was further supported by the amplified inhibitory effect on the expression of osteoblastic markers exerted by adipocyte-conditioned media in low [Na+] conditions. Finally, the analysis of cytoskeleton by immunofluorescent microscopy showed that low [Na+] was associated with disruption of tubulin organization in hMSC-derived osteoblasts, thus suggesting a negative effect on bone quality. These findings add new evidence that hyponatremia should be carefully taken into account by clinicians because of its negative effects on bone, in addition to the known neurological effects, and indicate for the first time that impaired osteogenesis may be involved.

DOI: 10.1530/endoabs.37.EP285

EP286

Thalassemia-induced osteoporosis and bisphosphonate treatment: a systematic review and meta-analysis

Athanasios Tsartsalis[1], George Lambrou[2], Christos Savvidis[3], George Chrousos[2] & Antonis Kattamis[2]
[1]Department of Endocrinology and Diabetes, Naval Hospital, Athens, Greece; [2]1st Department of Pediatrics, University of Athens, Athens, Greece; [3]Department of Endocrinology and Metabolism, Hippocration General Hospital, Athens, Greece.

Introduction
Osteopenia and osteoporosis develop with aging in thalassemia patients despite clinical treatment therapy has improved. Bisphosphonates, which are potent inhibitors of osteoclastic bone resorption, have been recently used to correct the bone abnormality in thalassemia with encouraging results. Bisphosphonates are a class of drugs that prevent the loss of bone mass, used to treat osteoporosis and similar diseases. They are the most commonly prescribed drugs used to treat osteoporosis. Bisphosphonates act by inhibiting osteoclastic recruitment and maturation, preventing the development of monocyte precursors into osteoclasts, inducing osteoclast apoptosis and interrupting their attachment to the bone.
Scope
The scope of the present work was to meta-analyse available data concerning the role of bisphosphonates in thalassemia-induced osteoporosis.
Methods
A search was carried out to find relevant studies and reviews published up to date. The database used was Pubmed. The MeSH terms used were: bisphosphonate, thalassemia and/or anaemia, osteoporosis, which yielded 33 results. From those 22 has been selected for further processing as more relevant to the topic of study.
Results
Based on the meta-analysis of selected studies it appeared that bisphosphonates could prove an effective treatment for osteoporosis. In particular, zoledronic acid was effective in the treatment of osteoporosis, while clodronate did not appear to be equally effective. In total, bone mineral density as well as markers of bone remodelling (CTX, bALP, OPG, etc.) were higher in the bisphosphonate-treatment groups as compared to the placebo group.
Conclusions
Cross-examination of several studies suggests that bisphosphonates are to be considered as a therapeutic option for the treatment of thalassemia-induced osteoporosis.

DOI: 10.1530/endoabs.37.EP286

EP287

Bones in pseudohypoparathyroidism type 1a

Slavica Savic[1], Tanja Nisic[1], Tijana Lalic[1], Biljana Nedeljkovic-Beleslin[1,2], Mirjana Stojkovic[1], Marija Barac[1], Milos Stojanovic[1], Jasmina Ciric[1,2] & Milos Zarkovic[1,2]
[1]Clinic of Endocrinology, Diabetes and Metabolic diseses, Clinical Centre of Serbia, Belgrade, Serbia; [2]Faculty of Medicine, University of Belgrade, Belgrade, Serbia.

Pseudohypoparathyroidism type 1a (PHP1a) is disorder characterised by resistance to the biological actions of circulating parathyroid hormone (PTH) along with typical features of Albright's hereditary osteodystrophy (AHO). Tissue-specific imprinting of GNAS gene results in complete resistance to PTH in renal proximale tubule, but skeletal responsiveness to PTH appears intact, since Gαs is biallelically expressed in human bones. The objective of this study was to determine BMD, and its relation to PTH levels in a group of young adult patients with PHP1a (age range 19–32 years). BMD measurements (Hologic QDR 4500) at the lumbar spine (LS), total hip (TH) and femoral neck (FN) were obtained in five patients with PHP1a (diagnosis was based on presence of AHO features combined with multihormone resistance). All patients were diagnosed with this condition earlier, and treatment was begun between ages 4 and 21 years. Caracteristics of study patients: intact PTH levels ranged from 120.9 to 436 pg/ml (reflecting inadequate dosing of calcium and calcitriol); all patients were taking levothyroxine and TSH levels were mildly elevated (range 5.98–12.10 mIU/l); three subjects were GH deficient, and none recieved GH therapy. The mean BMD Z-score for the LS was −1.4 (range −2.6 to −0.6), which is not significantly different from normal. Three subjects had Z-scores out of ±1, range expected for the normative population, and one of them met the criteria for low BMD. The mean BMD Z-score for the TH was −1.1 (range −1.6 to −0.8), and for the FN was −0.8 (range −1.9 to 0.2), both not significantly different from normal controls. Our results show that subjects with PHP1a, despite significant secondary hyperparathyroidism, had normal bone mass, with exept of one subject (20%) who had low LS BMD. These results are somewhat conflicting with previous study wich demonstrated that bone mass is either normal or increased in PHP1a.

DOI: 10.1530/endoabs.37.EP287

EP288

Clinical risk factors for osteoporosis in type 1 diabetes

Monica Goia-Socol[1,2], Ileana Duncea[1,2], Mihai-Andrei Goia-Socol[1,3], Georgeta Hazi[2], Daniel-Corneliu Leucuta[4], Marius Pauliuc[1,2], Ioana Ilie[1,2] & Carmen Emanuela Georgescu[1,2]
[1]Department of Endocrinology, 'Iuliu Hatieganu' University of Medicine and Pharmacy, Cluj-Napoca, Romania; [2]Endocrinology Clinic, Cluj County Emergency Hospital, Cluj-Napoca, Romania; [3]Diabetes Center, Cluj County Emergency Hospital, Cluj-Napoca, Romania; [4]Department of Medical Informatics and Biostatistics, 'Iuliu Hatieganu' University of Medicine and Pharmacy, Cluj-Napoca, Romania.

Introduction
Type 1 diabetes secondary osteoporosis is an underdiagnosed condition and there are few studies that addressed the topic of clinical risk factors in this context, although, for a better diagnosis and management, it is of great importance to find such predictors.
Aim
To evaluate bone mineral density and parameters of bone metabolism in patients with type 1 diabetes in comparison with a group of healthy subjects and to determine possible risk factors for osteoporosis in the context of type 1 diabetes.
Patients and methods
102 patients with type 1 diabetes and 59 healthy controls (pre-menopausal women and men, aged between 20 and 55 years), matched by age, sex, and BMI were included in the study. All subjects with secondary causes of osteoporosis except type 1 diabetes and diabetic patients with stage 3 nephropathy or more (GFR <60 ml/min per 1.73 m^2) were excluded. Their lifestyle, personal and parental history were evaluated with a questionnaire, anthropometric measurements were made and DXA osteodensitometry was performed. Serum osteocalcin, intact PTH, 25(OH) vitamin D, total calcium, phosphorus and magnesium were determined.
Results
The risk for low BMD (at least a *Z* score equal or lower than −2.0 S.D. at any site) was 1.2 higher in type 1 diabetes (95% CI 0.43–3.33), however BMD was not significantly different between patients and controls ($P=0.88$ for lumbar spine and 0.56 for femoral neck).Type 1 diabetic patients had a median age of 28 and a median disease duration of 11.5 years. Median HbA1c was 8.1%. BMD for a disease duration over 10 years was significantly lower than that for 0.5-5 years ($P=0.008$, ANOVA). Diabetic nephropathy (stages 1 and 2) increased the risk for low BMD and was associated with a significant rise of PTH. Age was negatively associated with lumbar spine BMD and positively with PTH. BMI was positively associated with BMD at all sites.
Conclusions
The most important predictors for osteoporosis in our study were type 1 diabetes duration (over 10 years) and the presence of diabetic nephropathy. Age towards the upper limit of inclusion (i.e. 55 years old) or low BMI values (low/low normal) may complete an indication for performing DXA in type 1 diabetic patients. Long-term lifestyle measures that we found to be protective for osteoporosis were: avoiding coffee and alcohol consumption, regular exercise and an optimal metabolic control of diabetes.
Disclosure
This work was supported by the European Social Fund POSDRU 107/1.5/S/78702 project.

DOI: 10.1530/endoabs.37.EP288

EP289

Glucocorticoid induced osteoporosis; can we do more to prevent it?

Plaisanu Cristina[1], Iorgoveanu Vasilia[2] & Trifanescu Raluca[3]
[1]Carol Davila Medicine University, Bucharest, Romania; [2]Saint Mary Clinical Hospital, Bucharest, Romania; [3]'I.C Parhon' Endocrinology Institute, Bucharest, Romania.

Introduction
Osteoporosis is a well-known and extremely debated side effect of glucocorticoid therapy being able to generate vertebral fractures even at low doses. Our study highlights the need for better prevention through improved doctor-patient communication and correct implementation of available screening tools.
Methods
Since August–December 2014 we distributed to 85 rheumatic patients a self-compiled questionnaire. We recorded patient data and their awareness on current recommendations, osteoporosis screening/treatment information. Hospital's electronic database provided DXA and radiographic results.
Results
Study included 72/85 women, median age 57.5 years, 38/85 rheumatoid arthritis, 20/85 systemic lupus erythematous, and 27/85 other diseases, median disease duration 72 months. 55/85 (64.70%) received <7.5 mg/day, whilst 30/85 (35.29%) received >7.5 mg/day for >3 months. 40/85 (47.05%) have undergone a DXA and 24/40 (60%) have osteoporosis and bisphosphonate treatment. Only 51/85 (60%) is aware of this therapy risk. FRAX 10 years probability of osteoporotic fractures was >20% in 9/24 (37.5%) patients. Only 31/85 (36.47%) were aware that smoking cessation is recommended, 62/85 (72.94%) knew excessive alcohol intake must be avoided and 20/85 (23.52%) were aware of the need for weight-bearing activities. Only 50/85 (58.82%) have a radiographic imaging of the spine and 10/50 (20%) have vertebral fractures on radiography. 70/85 (82.35%) have received vitamin D supplements.
Conclusion
Study revealed a lack of proper screening for glucocorticoid osteoporosis and a high percentage of patients not aware of existing recommendations regarding lifestyle modifications needed for prevention. Clinicians should make more efforts for patient to properly understand this risk, to know the ways to diminish it and, last but not least, the utility of early diagnostic and treatment.
Disclosure
This work received financial support through the project entitled 'CERO – Career profile: Romanian Researcher', grant number POSDRU/159/1.5/S/135760, cofinanced by the European Social Fund for Sectoral Operational Programme Human Resources Development 2007–2013'.

DOI: 10.1530/endoabs.37.EP289

EP290

Barakat syndrome: an uncommon cause of hypocalcaemia

Teresa Rego, Fernando Fonseca & Ana Agapito
Endocrinology Department, Curry Cabral Hospital, Lisbon, Portugal.

Introduction
Barakat syndrome is a very rare disease and an uncommon aetiology of hypocalcaemia. Also known as HDR syndrome it is an autosomal dominant disorder characterised by hypoparathyroidism, sensorineural deafness and renal disease.
Clinical case
A 59-year-old Caucasian woman was admitted to our Endocrinology ward in May 2014 due to hypocalcaemia despite being medicated with oral calcium. At 35 years old a diagnosis of hypoparathyroidism was established in another hospital when she presented generalized seizures and cardiac failure. Intracranial basal ganglia calcification where revealed at that time and a diagnosis of hypocalcaemic miocardiopathy was established. At the present admission in our hospital, further history revealed progressive hearing loss for the last 20 years. Laboratory work up: Ca^{2+} 7.7 mg/dl (8.6–10.2 mg/dl), Pi 3.1 mg/dl (2.5–4.5), Mg^{2+} 1.9 mg/dl (1.6–2.3), PTH 1.3 pg/ml (12–88), and creatinine 1.10 mg/dl. Abdominal CT scan showed right kidney hypoplasia. DNA sequence analysis revealed on exon 5 of *GATA3* gene a heterozygotic mutation c.1043T > C (p.Leu348Pro) that confirmed the diagnosis of Barakat syndrome. We observed one of the two adult sons and the adult daughter of this patient. Hypocalcaemia due to hypoparathyroidism and neurosensorial bilateral deafness were documented in both. Genetic study of this offspring is in course.
Comments
Barakat syndrome may present a variable phenotype. Renal manifestations are the most heterogeneous and usually determine disease prognosis. This patient has the classical triad. The severity of hypocalcaemia since young age and subsequent irreversible cardiac involvement were determinant for prognosis. Timely diagnosis and appropriate hypocalcaemia treatment are paramount. Genetic screening of relatives takes particular relevance in this context.

DOI: 10.1530/endoabs.37.EP290

EP291

The diagnostic value of parathyroid hormone washout after fine-needle aspiration in patients with primary hyperparathyroidism

Fotini Adamidou[1], Panagiotis Anagnostis[1], Vasileios Champidis[1], Simoni Katergari[1], Georgios Zacharioudakis[2] & Marina Kita[1]
[1]Department of Endocrinology, Hippokration Hospital of Thessaloniki, Thessaloniki, Greece; [2]Fifth Department of Surgery, Hippokration Hospital of Thessaloniki, Aristotle University of Thessaloniki, Thessaloniki, Greece.

Introduction
Commonly used pre-operative methods (ultrasonography and sestamibi scan) to localize the culprit parathyroid gland(s) in patients with primary hyperparathyroidism (PHPT), frequently yield false positive or false negative results. Parathyroid hormone (PTH) washout after fine-needle aspiration (FNA) may allow for a targeted surgical approach. The aim of this study was to test the diagnostic value of preoperative PTH washout after FNA in PHPT patients.
Methods/design
Retrospective study conducted in a tertiary centre. Ultrasound-guided FNA was performed if a structure compatible with a parathyroid adenoma was found on cervical ultrasound. A PTH washout cut-off value was considered diagnostic if it was higher than the concomitant serum PTH value.
Results
Twenty-nine patients (2 (6.8%) males, mean age 58.6 ± 9.1 years) were included. Mean pre-operative serum PTH levels were 194.2 ± 176.8 pg/ml (normal: 10–53), while serum calcium and 25-hydroxy-vitamin D levels were 11.5 ± 1.4 mg/dl (normal: 8.8–10.6) and 24.1 ± 20.5 ng/ml (deficiency: < 20 ng/ml) respectively. Post-operative serum PTH and calcium levels were 45.9 ± 26.3 pg/ml and 9.04 ± 0.7 mg/dl respectively. A single adenoma was identified in 26 (89.7%) patients and a double adenoma in 1 (3.4%). Two (6.9%) patients were harbouring an ectopic parathyroid adenoma (upper mediastinal and intrathyroid). Twenty-four patients (82.7%) had elevated PTH washout concentrations (mean values: 2009.5 ± 1417.6 pg/ml). True positive and false negative results were 24 and 4 respectively. The sensitivity, specificity and positive predictive value (PPV) were 85.71, 100, and 100% respectively. Interestingly, in ten out of 12 patients with a negative sestamibi scan, the PTH washout yielded a truly positive result.
Conclusions
Elevated PTH washout concentrations after ultrasound-guided FNA is an highly accurate diagnostic tool in identifying parathyroid adenomas and guiding parathyroid surgery.

DOI: 10.1530/endoabs.37.EP291

EP292

Relationship between vitamin D supply and healing in patients with hip fracture

Erzsebet Toldy, Antal Salamon, Balazs Hepp, Akos Matrai, Csaba Biro, Katalin Agota, Emoke Fata & Zoltan Locsei
Markusovszky Hospital, Szombathely, Hungary.

Background
Vitamin D (VD) deficiency is important risk factor of fractures. Yet, the relation of serum 25-hydroxyvitamin D (25OHD) levels and recovery of fractures is poorly studied. Our aim was to investigate the VD supply in hip fractures also with regard to lifestyle and other clinical (malignancy, kidney and liver disease, osteoporosis) conditions.
Method
25OHD (protein binding assay, Cobas, Roche) and parathyroid hormone (PTHi) (electrochemiluminescence immunoassay, Cobas, Roche) levels of 202 patients (67 men and 135 women) with hip fracture (age 75 ± 12 years) and 102 age-matched persons with active lifestyle, as controls were investigated.
Results
VD deficiency and secondary hyperparathyroidism occurred significantly more frequently in patients with hip fracture than in the control group (73% vs 36% and 33% vs 12% respectively). Patients with better condition after surgery showed significantly higher 25OHD (median with interquartilis ranges: 44 (28–72) vs 15 (9–43) nmol/l; $P < 0.001$) and lower PTHi (51 (35–64) vs 63 (48–88) pg/ml, $P < 0.05$) levels than patients with bad condition. 31 patients who died after surgery (median survival time: 19 (5–52) days) had lower 25OHD levels than those who survived (23 (9–43) vs 33 (17–57) nmol/l) without significant difference in PTHi levels. These results were independent of chronic disorders.
Conclusion
The correlation between 25OHD levels and better postoperative condition confirm the importance of VD substitution in prevention, as well as in healing, and in increased survival rate.

DOI: 10.1530/endoabs.37.EP292

EP293

An oral high dose of cholecalciferol restores vitamin D status in deficient postmenopausal HIV-1 infected women independently of protease inhibitors therapy

Jessica Pepe, Ivano Mezzaroma, Alessandra Fantauzzi, Mario Falciano, Alessandra Salotti, Mario Di Traglia, Daniele Diacinti, Sara Belcastro, Sara Piemonte, Cristiana Cipriani & Salvatore Minisola
Sapienza University, Rome, Italy.

Introduction
The best repletion and maintenance dosing regimens with cholecalciferol in vitamin D deficient HIV-1 patients remain unknown. Protease inhibitors (PIs) have been shown to inhibit vitamin D 1α- and 25α-hydroxylation in hepatocyte and monocyte cultures. We therefore evaluated the effect of a single high dose of cholecalciferol in vitamin D deficient HIV-1 postmenopausal women undergoing treatment with highly Active Anti-Retroviral Therapy (cART), with and without PIs.
Methods
Forty HIV-1 postmenopausal women treated with cART, with hypovitaminosis D (< 20 ng/ml), were enrolled. We measured serum changes of 25-hydroxyvitamin D (25(OH)D), 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), parathyroid hormone (PTH), serum calcium and urinary calcium excretion following a loading dose of 600 000 IU of cholecalciferol after 3, 30, 60, 90, and 120 days.
Results
The sample was divided according to the presence PIs (group A, $n = 20$) or absence (group B, $n = 20$). There were no significant differences between the two groups at baseline (mean 25(OH)D group A 13.93 ± 3.85 vs group B 12.94 ± 3.86 ng/ml, P = NS). The cART scheme was not modified during the study period. We did not find any significant changes in the two groups, as regards: the mean CD4 values, the HIV RNA values, and the body mass index. A significant increase in mean 25(OH)D and $1,25(OH)_2D$ levels at day 3 and throughout the entire observation period was found in both groups ($P < 0.001$). PTH levels concomitantly decreased in both groups ($P < 0.001$). Mean albumin-adjusted serum calcium increases with respect to baseline were significant only at days 3 and 30 for both groups ($P < 0.01$). There were no significant differences between the groups at any time, by two-way RM ANOVA.

Conclusions
An oral dose of 600 000 IU of cholecalciferol in HIV-1 postmenopausal women rapidly increases 25(OH)D and $1,25(OH)_2D$ levels reducing PTH levels, regardless of the presence of PIs in the cART scheme.

DOI: 10.1530/endoabs.37.EP293

EP294

May the polymorphism of low molecular weight protein tyrosine phosphatase modulate metabolic and bone remodelling parameters associated with osteoporosis?

Joana Freitas[1,2], Cristina Monteiro[3], Ana Paula Barbosa[2,4], Fátima Batista[3], Maria José Laires[3], Manuel Bicho[1,2] & Mário Rui Mascarenhas[2,5]
[1]Institute for Scientific Research Bento Rocha Cabral, Lisbon, Portugal; [2]ISAMB, FMUL, Lisbon, Portugal; [3]CIPER, FMH-UL, Lisbon, Portugal; [4]Clinic of Endocrinology, Diabetes and Metabolism, Lda, Lisbon, Portugal; [5]Department of Endocrinology, Diabetes and Metabolism, HSMaria-CHLN, Lisbon, Portugal.

Aims
To study the association of protein tyrosine phosphatase (LMW–PTP/ACP1) polymorphism with bone mineral density and metabolic parameters of bone remodelling.
Methods
BMD (g/cm^2) was measured by DEXA in 760 subjects: 448 normal BMD (359F/89M; 49.7 ± 12.9 years; $30.2 \pm 5.4\ kg/m^2$) and 312 osteoporosis (265F/47M; 63.9 ± 10.4 years; $27.16 \pm 4.4\ kg/m^2$). Metabolic bone remodelling parameters were analyzed: LDL, HDL, total cholesterol, triglycerides, HOMA, alkaline phosphatase (AP), and osteocalcin. ACP1 activity was measured by spectrophotometry. ACP1 polymorphism was evaluated by PCR.
Results
Association was found between the genetic polymorphism of ACP1 and its enzymatic activity with higher values for genotypes AC + BC, intermediate values for BB and lower values for AA + AB. Osteoporosis: i) increased LDL, total cholesterol, AP, osteocalcin and ACP1, and decreased HOMA; ii) association between genotypes BB + BC + AC and increased total cholesterol, LDL, and ACP1; and iii) positive correlation between AP and LDL, total cholesterol, and osteocalcin. Normal BMD: i) association between genotypes BB + BC + AC (intermediate and higher ACP1 activity) and increased ACP1 and decreased AP and ii) positive correlation between AP and osteocalcin and HOMA. Only correlations of AP with LDL and total cholesterol remained significant when analyzed separately AA + AB individuals.
Conclusion
In osteoporosis, ACP1 polymorphism appears to modulate some metabolic parameters associated with a decrease in BMD, including total cholesterol, LDL, and ACP1 activity.

DOI: 10.1530/endoabs.37.EP294

EP295

Pancreatitis in familial hypocalciuric hypercalcaemia

Iulia Potorac[1], Olivier Malaise[2], Adrian Daly[1] & Albert Beckers[1]
[1]Department of Endocrinology, CHU de Liège, University of Liège, Liège, Belgium; [2]Department of Rheumatology, CHU de Liège, University of Liège, Liège, Belgium.

Familial hypocalciuric hypercalcaemia (FHH) is a characteristically asymptomatic condition that is caused principally by calcium sensing receptor gene (CASR) mutations and less frequently by GNA11 or AP2S1 mutations. We report a case of recurrent symptomatic pancreatitis in an FHH patient. The 17-year-old patient was hospitalized with abdominal pain and raised pancreatic enzymes due to acute pancreatitis. The only predisposing factor on investigation was a very elevated serum calcium level (3.3 mmol/l; NR: 2.15–2.60). This was associated with concomitantly moderately elevated PTH (33 ng/l; NR: 4–26), normal 25-OH vitamin D (44 ng/ml; NR: 30–80), elevated $1,25(OH)_2$ vitamin D (133 pg/ml; NR: 23–109), and undetectable urinary calcium. Family history revealed that the patient's grandmother was also known to suffer from hypocalciuric hypercalcaemia, and that hypercalcaemia had been found in the patient's mother, uncle, brother and sister. CASR sequencing revealed the patient (and family members) to be heterozygotic for a R185Q mutation, previously suggested to be a dominant negative mutation and leads to higher calcium levels than other known CASR mutations. Cinacalcet treatment lowered serum calcium to 2.95 mmol/l and the patient has not presented new pancreatitis episodes.

DOI: 10.1530/endoabs.37.EP295

EP296

Giant parathyroid adenoma with severe hypercalcaemia: case report

Cristina Spiroiu, Aurelian Emil Ranetti & Claudiu Nistor
Central University Military Hospital 'Dr Carol Davila', Bucharest, Romania.

Introduction
Parathyroid adenomas are the main cause of primary hyperparathyroidism. They are usually small – weighing <1 g – and not easy to find – requiring meticulous imaging studies for localisation. Giant adenomas are uncommon; large tumours and high levels of PTH raise the suspicion of parathyroid malignancy.
Case presentation
A 68-year-old female presented in our clinic with polydipsia, poliuria, nausea, weight loss, and extreme muscular weakness – she wasn't able to walk – and depressive mood. Clinical exam revaled dehydration and right cervical mass. Calcium was 21 mg/dl and PTH was 2238 pg/ml. The patient was also vitamin D deficient – 25OH vitamin D 14 μg/l. Radiographic study showed fracture of the first lumbar vertebra, CT scan showed multiple osteolytic areas of the skull. Osteodensitometry demonstrated osteoporosis (lumbar spine T score -2.9 S.D. and distal radius T score -6.7 S.D.). Ultrasonography revealed a hypoechoic inhomogeneous mass, 38/30/45 mm, laterally and caudally to the right thyroid lobe. Parathyroid scintigraphy (99Tc-MIBI) demonstrated a large area of high uptake in that region. The patient received intravenous fluids, loop diuretic, i.v. bisphosphonate (zoledronate) and calcitonin to reduce the level of calcium, then she was successfully operated. Calcemia dropped after surgery and it was managed with i.v. calcium and alpha calcidol. Mild hypocalcemia persisted for more than 6 months thereafter and so did the high levels of PTH, that raised to 506.5 pg/ml, then returned to normal – the hungry bones syndrome. The pathologic diagnosis was benign parathyroid tumour – parathyroid adenoma.
Conclusions
This is a rare case of giant parathyroid adenoma. The peculiarities of the case are the size of the tumour, the very high level of calcium and PTH – suggesting a malignant tumour, and the persistence of high levels of PTH and hypocalcemia months after surgery.

DOI: 10.1530/endoabs.37.EP296

EP297

Primary hypoparathyroidism is common in adult patients with β-thalassemia and protect patients from osteoporosis

Anna Ansaloni[1], Francesca Ferrara[3], Chiara Diazzi[1,2], Antonello Pietrangelo[3], Manuela Simoni[1,2] & Vincenzo Rochira[1,2]
[1]Unit of Endocrinology, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy; [2]Azienda USL of Modena, Modena, Italy; [3]Unit of Internal Medicine, Research Center 'Mario Coppo', University Hospital Policlinico, Modena, Italy.

Introduction
β-thalassemia (bT) is associated to several endocrine abnormalities mainly due to iron overload. With the increase in bT-patients life expectancy, due to progresses in iron chelation therapy, more patients enter into adulthood than in the past and the prevalence of endocrine diseases is being reconsidered. The aim of the study is to investigate the prevalence of primary hypoparathyroidism (pHPT) in adult bT-patients and to characterize the relative clinical phenotype with particular regard to bone health.
Methods
We enrolled 26 adult patients with major or intermedia bT (12M and 14F; mean age ± S.D. of 38.1 ± 7.5 years). Serum PTH, 25-hydroxyvitamin D (25OHD), calcium, phosphorous, albumin, bone turnover markers, and bone mineral density (BMD) by dual-energy X-ray absorptiometry (Hologic) at lumbar and femoral site were measured.

Results
pHPT (PTH <15 pg/ml) was found in seven of the 26 patients (27%). Of them, four patients (57%) had hypocalcemia and two were on chronic calcium therapy. Lumbar BMD was significantly higher in patients with pHPT (0.884 ± 0.189 g/cm^2) than in patients without pHPT (0.731 ± 0.124 g/cm^2) ($P=0.023$). No significant difference was found in femoral BMD, even though a trend for higher BMD was present in pHPT (0.704 ± 0.117 vs 0.670 ± 0.143 g/cm^2 in pHPT and no-pHPT respectively) ($P=0.578$). The prevalence of osteoporosis was higher in patients without pHPT (68%) than in patients with pHPT (29%). Two patients had a history of bone osteoporotic fractures and both of them did not present pHPT. Bone turnover markers were no different in the two groups.
Conclusions
The prevalence of pHPT in adult bT-patients is higher if compared to that observed in pediatric bT-patients, the latter ranging from 8 to 11%. Moreover we found an higher prevalence of pHPT compared to that reported in literature on adult bT patients. As expected, pHPT seems to exert a protective role on the development of osteoporosis in these patients.

DOI: 10.1530/endoabs.37.EP297

EP298

Renal calcification in hypoparathyroid patients treated with calcium and vitamin D: can biochemistry help?

Sivatharshya Pathmanathan[1], Scott Tolhurst[2], Emma Illingworth[1], Claire Higham[1], Peter Trainer[1] & Phillip Monaghan[2]
[1]Department of Endocrinology, The Christie NHS Foundation Trust, Manchester, UK; [2]The Christie Pathology Partnership, The Christie NHS Foundation Trust, Manchester, UK.

Introduction
Hypoparathyroidism is most commonly observed following neck surgery and is characterized biochemically by deficient parathyroid hormone (PTH) and hypocalcaemia alongside hyperphosphataemia and reduced 1,25-dihydroxyvitamin D. Standard treatment with oral calcium and vitamin D aims to maintain serum calcium within the low-normal range whilst avoiding hypercalciuria due to over replacement. However, concerns remain over the presence of hypercalciuria and the associated risk of renal calcification.
Aim
To assess whether serum and urine biochemical parameters are associated with the presence of renal calcification in hypoparathyroid patients on Alfacalcidol therapy.
Method
A 12-month audit of the laboratory database was undertaken of paired requests for 24-h urine calcium (24 h-Ca), spot calcium:creatinine ratio (Ca:Creat), serum calcium, phosphate, urea, and creatinine. A review of case notes was performed to confirm aetiology of hypoparathyroidism, Alfacalcidol dose and results of renal ultrasound scan (USS).
Results
A total of 34 patients were identified as having hypoparathyroidism and receiving Alfacalcidol therapy. 24 h-Ca and Ca:Creat were not-normally distributed, however significant associations were found between 24 h-Ca and Ca:Creat when log-transformed (linear regression β-coefficient $=0.64$; 95% CI 0.36–0.92; $P<0.001$, $\beta=0.63$). 17 patients had documented hypercalciuria evidenced by elevated 24 h-Ca (five patients), Ca:Creat (eight patients), or both (four patients). 13 patients had undergone renal USS; four had evidence of renal calcification. Interestingly, these four patients each had an elevated Ca:Creat, in contrast with only one patient having elevated 24 h-Ca.No patient had hypercalcaemia. However, 20 patients had low, or low-normal serum adjusted calcium (Ca <2.2 mmol/l); nine of these patients having documented hypercalciuria evidenced by an elevated 24 h-Ca (78% of patients) or Ca:Creat (89% of patients).
Conclusion
Ca:Creat appears a sensible and convenient marker for the follow-up of patients on long term Alfacalcidol therapy to determine associated risk of renal calcification.

DOI: 10.1530/endoabs.37.EP298

EP299

Parathyroid tissue in ectopic thyroid tissue

João Silva, Catarina Ivo, Mafalda Marcelino, Dolores Passos, Hélder Simões, Luís Lopes & João Jácome de Castro
Armed Forces University Hospital, Lisbon, Portugal.

Introduction
Postmortem studies have shown that a fifth parathyroid gland may be present in about 5% of patients with hyperparathyroidism. 1% of parathyroid glands are located in thyroid tissue. There's a prevalence of 7–10% of thyroid ectopic tissue.
Case report
A 53-year-old male, submitted to bilateral nephrectomy due to a Grawitz tumour at the age of 25. Under haemodialysis since then (with a rejected renal transplant in the past), he was recently referred to our department with a tertiary hyperparathyroidism diagnosis. Treated intra-hemodialysis with alfacalcidol 0.25 µg and cinacalcet. Analytically had a PTH 1604 pg/ml, calcium 9.5 mg/dl, phosphorus 5.6 mg/dl, and creatinine 11.4 mg/dl. Cervical ultrasound did not identify parathyroid gland and thyroid scintigraphy suggested parathyroid adenoma in the bottom right. PET-scan showed bone lesions suggestive of brown tumours. The patient was submitted to surgery and has removed four parathyroid glands (9–20 mm) with an histology of 'nodular hyperplasia of the parathyroid'. Was also removed a fifth nodule located in the lower left region with 9 mm, described as 'focus of parathyroid in parenchyma thyroid (intra-thyroid parathyroid?)'. Three months after surgery he's treated with 1 g of calcium carbonate $(3+3+3)$ and 0.25 µg calcitriol $(1+0+1)$, with PTH 139 pg/ml, calcium 8.2 mg/dl, and phosphorus 2.6 mg/dl.
Conclusions
In this patient despite scintigraphy suspicion of a functioning parathyroid adenoma, since it is a tertiary hyperparathyroidism, we chose surgical exploration with resection of all parathyroid glands. It was found a fifth focus of parathyroid tissue within an ectopic thyroid tissue. This case presents the association of three relatively rare situations: supernumerary parathyroid gland, in thyroid tissue in an ectopic location.

DOI: 10.1530/endoabs.37.EP299

EP300

Anti-diabetic treatment as an additional factor in a FRAX based evaluation of osteoporotic fracture risk

Maria P Yavropoulou, Athanasios Mousiolis, Vasiliki Kolokouri, Pelagia Kolimpianaki, Athina Dimitriou, Petros Papalexis, Michael Daniilidis & Kalliopi Kotsa
Department of Endocrinology and Diabetes, AHEPA University Hospital, Thessaloniki, Greece.

Background
The present study is designed to assess the incidence of osteoporotic fractures and the associated risk factors and particularly those used to predict the 10-year fracture risk in FRAX score based on data gathered in general practitioner's records of rural Greece.
Patients and methods
We conducted a retrospective analysis of all patients with osteoporosis presented between October 2013 and December 2014. Data from medical records including gender, age, previous history of low energy fractures (spine, and distal radius), past medical history, and medication use with specific reference to treatment with bisphosphonates and glucocorticoids were obtained. Patients with metabolic bone disease other than osteoporosis were excluded from the final analysis.
Results
One hundred and sixty seven patients (127 women and 40 men) aged between 44 and 90 years old were included in the final analysis. Twenty-seven percent of the study population ($n=45$) had sustained a low energy fracture and only 43% of them had received anti-osteoporosis treatment. Regarding concomitant medications only anti-diabetic treatment was significantly associated with the presence of osteoporotic fracture ($F=4.260$, $P=0.042$), and had a considerable effect on the 10-year risk of major osteoporotic and hip fractures in drug-naïve patients.
Conclusion
Anti-diabetic treatment should be taken into consideration when evaluating fracture risk in osteoporotic patients.

DOI: 10.1530/endoabs.37.EP300

EP301

A giant parathyroid cyst manifesting with a neck mass and hypercalcaemic crisis

Fotini Adamidou, Christina Manani, Vassilis Champidis, Panagiotis Anagnostis, Apostolos Kambaroudis & Marina Kita
Hippokration General Hospital, 49 Konstantinoupoleos Street, Thessaloniki 54642, Greece.

Introduction
Functional parathyroid cysts represent an uncommon cause of primary hyperparathyroidism (PHPT) and an even rarer cause of a cervical mass.
Case report
A 57-year-old woman was referred to our department following emergency treatment of hypercalcaemic crisis (serum calcium 16.4 mg/dl) with i.v. hydration and zoledronic acid. She was found to have multiple vertebral fractures by plain radiographs one month previously. Despite being diagnosed and treated with cinacalcet for PHPT for a year prior to these events and a neck mass was noted, it was considered a cystic thyroid nodule. At presentation she had generalized weakness and left-sided neck discomfort with pressure symptoms. Her corrected serum calcium was 13.1 mg/dl, phosphate 0.9 mg/dl, PTH 330 pg/ml, alkaline phosphatase 260 (ULN 220 U/l), and kidney function was normal. Past history was notable for partial thyroidectomy in the 1970s. On examination, a firm, fixed cervical mass was palpable from the sternal notch to the jaw angle. On ultrasound, the mass was cystic with various septa and measured $9\times4\times4$ cm. Needle aspiration of the cyst evacuated 45 ml of hemorrhagic fluid, with PTH washout levels measuring 570 pg/ml. Within the next 2 weeks, a hematoma formed that resolved uneventfully, but the cyst recurred almost to its original dimensions, again causing local pressure. At surgery, the cyst measured $6.4\times4\times4$ cm and histology was consistent with hemorrhagic cystic necrosis of parathyroid adenoma surrounded by an intact thick (0.2–0.5 cm) fibrous capsule without evidence of local invasion. Postoperatively, serum calcium and phosphate were 8.6 and 3.8 mg/dl respectively. The patient remains normocalcemic on calcium and vitamin D supplementation 9 months after surgery.
Conclusion
This case highlights that a large functional parathyroid cyst can elude diagnosis because of its rarity; however, early identification is crucial for proper patient management.

DOI: 10.1530/endoabs.37.EP301

EP302

Observational study of PTH secretion dynamics in patients with secondary hyperparathyroidism

Natalia Karlovich
Belarusian State Medical University, Minsk, Belarus.

The aim was to analyse dynamics of PTH secretion in dialysis patients during different period of observation and to determine factors of secondary hyperparathyroidism progression. We examined 92 patients, 52f, 40m; age 47.2 ± 11.4 years; dialysis duration 4.9 ± 3.9 years; mean observational period 8.9 ± 4.3 months (6–24). Serum PTH, 25(OH)D3, osteocalcin (OC), C-terminal telopeptide of type I collagen (β-CTx), alkaline phosphotase (ALP), calcium (Ca), and phosphorus (P) were measured initially and at the end of observation. All patients were recommended to follow low-phosphate diet and 74.4% received calcium carbonate. PTH level was 559.6 ± 552.5 initially and 603.9 ± 581.6 pg/ml at the end of observation, $P=0.251$. Frequency of high, normal uremic and low PTH levels was 55.4% vs 57.6%, 20.7% vs 21.7% and 23.9% vs 20.7% respectively ($P>0.05$). P decreased from 2.34 ± 0.67 to 2.14 ± 0.60 mmol/l, $P=0.0003$. In patients with initial hypercalcaemia PTH increased from 525.3 ± 518.4 to 616.2 ± 606.2 pg/ml, $P=0.03$. PTH level at the end of observation correlate with age ($r=-0.25$), OC ($r=0.58$), β-CTx ($r=0.76$), and ALP ($r=0.40$). Strong correlation was found with the initial PTH ($r=0.84$). At the end of observation PTH decreased in 40 patients (43.5%), mean decrease 204.6 ± 250.1 pg/ml; increased in 52 patients (56.5%), mean increase 235.6 ± 274.5 pg/ml. Subgroups with decreased and increased PTH didn't show differences of demographic data, levels of Ca, P, and bone turnover markers. Comparison of initial and repeated PTH level in subgroups with duration of observation 6, 9, 12, and >12 months didn't reveal significant changes. We can assume that in dialysis patients with stable parameters of Ca, P, and bone turnover markers in the absence of therapeutic intervention of secondary hyperparathyroidism PTH level remains unchanged during period of observation up to 12 months and even more. In such patients reasonable interval of PTH measurement should be 6–12 months. Initial level of PTH is the most important predictor of parathyroid function dynamics. Young age, high Ca, P, and bone turnover markers levels are another factors influencing secondary hyperparathyroidism progression.

DOI: 10.1530/endoabs.37.EP302

EP303

Fragility fractures as the initial manifestation of indolent systemic mastocytosis

Evangeline Vassilatou[1], Nickolas Gavoyiannakis[3], Alexia Chatzipetrou[3], Christoforos Koulias[3], Michael Makris[3], Eustathios Garoflos[1], Dimitrios Hadjidakis[1,2], Dimitrios Rigopoulos[4] & George Dimitriadis[2]
[1]Endocrine Unit, 2nd Department of Internal Medicine–Propaedeutic, 'Attikon' University Hospital, Athens, Greece; [2]2nd Department of Internal Medicine–Propaedeutic, 'Attikon' University Hospital, Athens, Greece; [3]Mastocytosis Outpatient Clinic, Allergy Unit 'D. Kalogeromitros', 2nd Department of Dermatology and Venereology, 'Attikon' University Hospital, Athens, Greece; [4]2nd Department of Dermatology and Venereology, 'Attikon' University Hospital, Athens, Greece.

Introduction
Systemic mastocytosis (SM) is a rare disorder characterised by clonal proliferation of abnormal mast cells in several tissues, most often skin and bone marrow. Indolent systemic mastocytosis (ISM) is the commonest disease variant in adults, characterised by very low rate of mast cell proliferation. SM has been recognised as a cause of secondary osteoporosis.
Objective
To evaluate bone mineral density and fragility fractures in ISM patients.
Methods
Fourteen patients (nine women and seven premenopausal), aged 27–63 years (43.4 ± 11.8) diagnosed according to World Health Organization criteria were studied retrospectively. Clinical and biochemical data and bone mineral density (BMD) measurements by dual X-ray absorptiometry at the lumbar spine, the total proximal femur and the lower one-third radius were analysed. *T*-score was used to define osteopenia (<-1 to >-2.5 S.D.) or osteoporosis (-2.5 S.D. or lower) in postmenopausal women or men older than 50 years, and *z*-score <-2.0 for low BMD in younger men and premenopausal women, according to the International Society for Clinical Bone Densitometry. No patient reported other diseases or use of treatments known to affect bone or mineral metabolism, at initial assessment.
Results
Two patients (14.3%) had osteoporosis, two patients (14.3%) had osteopenia and seven patients (50%) had low BMD. BMD was generally lower at the spine than at the hip. Three patients (21.4%) reported fragility fractures: a 43-year-old premenopausal woman and a 38-year-old man had vertebral fractures, while a 31-year-old premenopausal woman had non-vertebral fractures. None of the patients with fragility fractures had cutaneous mastocytosis and only one of them reported a mild episode of anaphylaxis.
Conclusion
Bone involvement is frequent in ISM patients and may be the initial manifestation. Osteoporotic fractures of unknown aetiology should lead to the suspicion of SM particularly in individuals younger than 50 years.

DOI: 10.1530/endoabs.37.EP303

EP304

Evaluation of clinical and biochemical features of patients with atypical parathyroid adenoma: a retrospective study

Sefika Burcak Polat[1], Mehmet Kilic[2], Cevdet Aydin[1], Didem Ozdemir[1], Nuran Sungu[3], Reyhan Ersoy[1] & Bekir Cakir[1]
[1]Endocrinology and Metabolism Department, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey; [2]General Surgery Department, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey; [3]Pathology Department, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey.

Introduction
Primary hyperparatyhyroidism (PHPT) is usually caused by single or multiple adenomas and cancer is rare accounting for $<1\%$ of all presentations. The presence of certain cytological and architectural features such as adherence to adjacent organs, a solid growth pattern, broad bands of fibrosis, cytological atypia, and an irregular growth contour do not indicate malignancy but are recognised as atypical features encountered more commonly in malignant than benign tumours. Tumours that demonstrate these atypical features and do not fulfill criteria for carcinoma can be classified as atypical adenomas. Herein we aimed to evaluate the clinical and biochemical features of the patients histopathologically diagnosed with an atypical parathyroid adenoma.

Method
Our endocrine database was searched retrospectively for the patients with operated PHPT and diagnosed with atypical adenoma. Demographic, clinical, and biochemical data of the patients were recorded. A control group was formed from the patients who were also operated with the diagnosis of PHPT and classical parathyroid adenoma was detected histopathologically.
Results
There were 16 patients in the atypical adenoma group and thirty patients in the control group. Age and gender distribution of the patients were similar in between groups with female predominance. Serum Ca and P levels were also similar where as preoperative serum PTH, ALP, and urinary Ca excretion were significantly higher in patients with atypical adenoma ($P<0.001$, $P<0.001$, and $P=0.021$ respectively). Adenoma size was significantly higher in the atypical adenoma group compared to controls ($P=0.006$) and cystic degeneration and isoechoic appearance on USG were more prevalent among the atypical adenomas ($P=0.016$).
Conclusion
Preoperatively high PTH, ALP, and urinary Ca levels may be predictive for atypical adenoma or carcinoma within a patient being evaluated for PHPT. The surgeon might prefer enbloc parathyroidectomy instead of minimal invasive surgery in such cases with more strict postoperative follow up.

DOI: 10.1530/endoabs.37.EP304

EP305

Investigation of the relationship between type 2 diabetes and osteoporosis

Nada Boughanmi, Sonia Rekik, Hela Sahli, Elhem Cheour & Mohamed Elleuch
La Rabta Hospital, Tunis, Tunisia.

Introduction
Diabetes is often associated with complications and comorbidities. Osteoporosis (OP) is increasingly recognised as a significant comorbidity of type 2 diabetes mellitus (T2DM). The aim of this study was to determine the prevalence of OP in postmenopausal women with T2DM and to assess the association between T2DM and bone mineral density (BMD).
Methods
This cross-sectional study was carried out in 50 postmenopausal women with type T2DM and 50 age-matched non-diabetic women. Medical and lifestyle characteristics were recorded. BMD was measured in lumbar spine and femoral neck by dual-energy X-ray absorptiometry.
Results
Prevalence of OP in subjects with T2DM was 48%, whereas 30% of the non-diabetic subjects had OP ($P=0.002$). Patients with lumbar and/or hip osteoporosis were older ($P=0.004$), had a lower BMI ($P<0.001$) and had a longer duration of disease ($P<0.001$). BMD at the hip was positively correlated with BMI ($P<0.001$). Age ($P=0.004$), duration of diabetes ($P<0.001$), mean HbA1c levels ($P=0.01$), the presence of retinopathy ($P=0.04$) were negatively associated with BMD at the hip and lumbar spine. No correlation was found between BMD and presence of microalbuminuria, neuropathy, peripheral artery disease, cerebrovascular event, and coronary artery disease.
Conclusion
We found a high prevalence of osteoporosis in postmenopausal women with T2DM. The insufficiency of insulin and the decreased insulin sensitivity are important causes for OP in the patients with T2DM.

DOI: 10.1530/endoabs.37.EP305

EP306

Intraoperative parathyroid hormone monitoring during parathyroidectomy: description of our clinical experience

Mariana Tomé[1], Guillermo Martinez De Pinillos[2], Mariola Méndez[2], Eyvée Arturo Cuéllar[2], Fernando García[2], Ignacio Fernández López[2], Ignacio Fernández Peña[2], Juan Manuel García De Quirós[2], Juana Hidalgo[2], Margarita Rivas[2], Santiago Durán[2] & Maria Victoria Cózar[2]
[1]Hospital Punta De Europa, Algeciras, Spain; [2]Valme University Hospital, Sevilla, Spain.

Introduction
Primary hyperparathyroidism is caused by a single adenoma in 85% of cases. This is why bilateral neck exploration seems to be a very aggressive procedure in a large number of cases. Intraoperative parathyroid hormone (IOPTH) monitoring could be a useful tool in primary hyperparathyroidism surgery allowing a less invasive surgical approach. The aim of our study is to evaluate the possible impact of the measurement of IOPTH during surgery.
Methods
Retrospective study in which we included all patients who underwent parathyroidectomy with IOPTH monitoring between 2008 and 2013. We considered the following variables: preoperative localization techniques; neck exploration (uni or bilateral); prediction of curative parathyroid resection by using MIAMI criteria (>50% drop from highest baseline IOPTH level at 10 min after excision) and cure (normal calcaemia 6 months after surgery). Subsequently, we compared this sample with a group of patients who underwent parathyroidectomy between 2000 and 2002 without IOPTH monitoring.
Results
We studied 115 patients (80.9% females; mean age 57.4 ± 14.1 years). In most cases Technetium-99m-sestamibi scintigraphy was the preferred localization technique (97.4% of patients) with positive result in 76.8% of scintigraphies. 76.5% of patients underwent unilateral neck exploration (100% of them were cured). Following MIAMI criteria we were able to predict curative resection in 97.2% of these patients. 93.9% of the total sample were cured after surgery. We compared this results with a series of 35 patients without IOPTH monitoring (74.3% females, 58.51 ± 9.1 years). We did not find significant differences in cure (93.9% vs 91.4%, $P=0.61$). However, in the second group 100% of patients underwent bilateral neck exploration (23.5% in IOPTH group, $P=0.0005$).
Conclusion
By monitoring IOPTH in focused parathyroidectomy it is possible to perform a less invasive surgical approach without reduction in cure rate.

DOI: 10.1530/endoabs.37.EP306

EP307

Hypercalcaemia in patient with primary hyperparathyroidism and acromegaly

Gordana Pemovska[1], Cvetanka Volkanovska Ilijevska[2] & Brankica Krstevska[1]
[1]Medical Faculty, University Clinic of Endocrinology, Diabetes and Metabolic Diseases, Skopje, Macedonia; [2]General City Hospital 8-mi Septemvri, Skopje, Macedonia.

Introduction
Hypercalcaemia in acromegaly can be a result of several pathophysiological mechanisms. Multiple endocrine neoplasia type 1 (MEN1) syndrome, mitogenic effect of hyperactivated GH–parathyroid gland axis, i.e. primary hyperparathyroidism and hypercalcaemia mediated by elevated 1,25-dihydroxyvitamin D should be considered.
Case report
We describe a case of acromegaly associated with primary hyperparathyroidism. A 52-year-old female was diagnosed with acromegaly due to GH secreting pituitary microadenoma. Evaluation at diagnosis showed normal levels of hormones other than GH and IGF1, and presence of hypertension and multinodular goiter (volume 80 mm^3). Because the patient denied surgery, treatment with cabergoline was administrated and a biochemical control was accomplished.
Within 1 year of the diagnosis laboratory data showed hypercalcaemia (serum calcium 1.51 mmol/l (1.10–1.40)) in the setting of elevated parathormone (PTH) levels (158 pg/ml (15–65)) and low levels of vitamin D (5.6 nmol/l (>25)). Bone densitometry detected osteoporosis limited to the right radius (*T* score value −4.0 S.D.). Analysis of 24-h urine showed normal calcium and phosphate excretion. This findings were consistent with diagnosis of primary hyperparathyroidism. Imaging and radioisotope studies identified enlarged thyroid gland, predominantly the left lobe with consequent tracheal compression, and higher radioisotope uptake in the lower pole of the left thyroid lobe. Surgical excision of left lower parathyroid gland and subtotal thyroidectomy was done. Histopathological examination confirmed hyperplasia of parathyroid and thyroid gland. After surgery, serum calcium normalised, PTH levels significantly reduced to 73.2 pg/ml. Vitamin D remained low (17.8 nmol/l) and TSH levels elevated to 27 mU/l (0.4–4) for which vitamin D and levothyroxine substitution was started.

Conclusion
The approach to hypercalcaemia in the course of acromegaly implies evaluation for several potential pathophysiological mechanisms, which in turn dictates the treatment strategy – parathyroidectomy vs biochemical control of acromegaly.

DOI: 10.1530/endoabs.37.EP307

EP308

The value of intraoperative sonographic evaluation of neck in primary hyperparathyroidsm: case report of preoperative double adenoma upgraded to triple intraoperatively

Fatih Kuzu[1], Dilek Arpaci[1], Guldeniz Karadeniz Cakmak[2], Rabia Uslu Erdemir[3], Mehmet Cabuk[3], Sevil Ilikhan Uygun[4] & Taner Bayraktaroglu[1]
[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Bulent Ecevit University, Zonguldak, Turkey; [2]Department of General Surgery, Faculty of Medicine, Bulent Ecevit University, Zonguldak, Turkey; [3]Deparment of Nuclear Medicine, Faculty of Medicine, Bulent Ecevit University, Zonguldak, Turkey; [4]Department of Internal Medicine, Faculty of Medicine, Bulent Ecevit University, Zonguldak, Turkey.

Background
Primary hyperparathyroidism (PHPT), caused by increased parathyroid hormone (PTH) secretion, leads to generalised disorder of bone metabolism characterised with hypercalcaemia and hypophosphatemia. Causes of PHPT include solitary parathyroid adenoma (80%), primary parathyroid hyperplasia (10–15%), and parathyroid carcinoma (1–2%). Other rare cause is double parathyroid adenomas (DPA) with frequency <1–2%, which can be sporadic or familial. DPA should be considered for persistent or recurrent PHTP cases.
Case report
A 45-year-old female patient with type 2 diabetes was admitted with weakness, fatigue, and generalized bone pain. She had a history nephrolithaisis five times in the last 2 years. In laboratory examination, serum calcium level was 12.3 mg/dl (8.8–10.6), phosphorus level was 2.9 mg/dl (2.4–5.1), albumin level was 4.1 g/dl (3.5–5.3), PTH level was 237 pg/ml (12–88), alkaline phosphatase was 99 IU/l (60–105 IU/l), 25-OH vitamin D level was 6.4 ng/ml (20–30 ng/ml), 24-h urine calcium was 483 mg/day, creatinine clearance was 75 ml/min, and prolactin level was 26 ng/ml (5–26 ng/ml). I.v. saline and furosemide treatment was administered. Bone densitometry measurement was showed osteoporosis. Neck ultrasound imaging revealed no abnormality in the thyroid gland with bilateral smooth, ovoid, hypoechoic lesion considered parathyroid adenomas at inferior contiguity of thyroid gland in size of $15\times11\times8$ mm on the right and $18\times12\times7$ mm on the left side. Tc99m-MIBI scan detected parathyroid adenoma in the lower part of the left thyroid lobe consistent with radioactivity uptake, while in the lower part of the right thyroid was suspicious. PTH level from fine needle aspiration material of parathyroid washout was measured 2097 pg/ml from the right side and 1989 pg/ml from left side. Hence, bilateral minimally invasive parathyroidectomy was intended to be performed, but the surgeon saw a third adenoma at retrosternal location by using intraoperative ultrasonography (US), all were removed and pathology report was consistent with parathyroid adenoma.
Conclusion
Intraoperative parathyroid evaluation by US plays an important role preventing patient from unnecessary surgery.

DOI: 10.1530/endoabs.37.EP308

EP309

Parathyroid hormone therapy for postoperative resistant hypocalcaemia

Safak Akin, Miyase Bayraktar & Alper Gurlek
Deparment of Endocrinology and Metabolism, Faculty of Medicine, Hacettepe University, Ankara, Turkey.

Introduction
No consensus guideline on the treatment of hypoparathyroidism. Hypoparathyroidism is a disease characterized by hypocalcaemia and insufficient PTH. Conventional therapy includes calcium and active vitamin D supplementation, often in large doses.
Case report
A 31-year-old woman presented with hypercalcemia. Serum calcium and phosphorus levels were 10.5 and 2.56 mg/dl respectively. The serum PTH level was increased (1619 pg/ml). The serum 25-OH vitamin D level was decreased (3.5 ng/ml). Her past medical history revealed osteoporosis (femur T score -4.0). Parathyroid USG showed left and right parathyroid adenomas. Double adenoma excision from left and right inferior sites and total thyroidectomy was performed. On pathological examination of thyroid was benign thyroid nodules. Double parathyroid adenomas was identified. Postoperative serum calcium level was 5.5 mg/dl. She recieved daily calcium gluconate infusions. Discharge with calcitriol and $CaCO_3$ with latest calcium level was 6 mg/dl. During follow-up, she was taken to internal medicine ward with symtomatic hypocalcaemia. Serum calcium, phosphorus, PTH, and 25-OH vitamin D levels were 5.2 mg/dl, 3.2 mg/dl, <3 pg/ml, and 5 ng/ml respectively. The doses were progressively increased up to 12 μg/day calcitriol. Under this tretatment serum calcium level was 6.9 mg/dl. Phosphorus level was 3.8 mg/dl. Follow-up, 20 μg teriparatide b.i.d. was added to the treatment. She has used teriparatide for a period of 10 months. At the end of teriparatide treatment, calcitriol reduced to 4.5 μg/day and calcimax D3 reduced 3×1 tb. Final control visit her calcium level was 8.5 mg/dl and phosphorus level was 4.1 mg/dl while taking calcitirol dose of 3.5 μg/day and calcimax D3 dose of 2×2 tb.
Conclusion
In our postoperative hypocalcaemic case, calcitriol dose reduced and calcium level increased after the teriparatide treatment. Teriparatide may be useful in postoperative resistant hypocalcaemia.

DOI: 10.1530/endoabs.37.EP309

EP310

Vitamin D deficiency and bone health in patients with learning disability

Abbi Lulsegged[1], Nataliya Zuyeva[1] & Rob Winterhalder[2]
[1]Kings College Hospital NHS Foundation Trust, Farnborough, Kent, UK; [2]Oxleas NHS Foundation Trust, Farnborough, Kent, UK.

There is limited data on vitamin D status in patients with learning disabilities. As a group they possess multiple risk factors for vitamin D deficiency including limited access to sunlight, problems with mobility and anticonvulsant use. We reviewed the data for 105 patients with learning disabilities grouped according to the severity of learning disability (profound, severe, moderate, and mild). Data was available on vitamin D and calcium levels, dose of vitamin D3 needed to correct the vitamin D deficiency with the aim of correcting above a minimum target level of 80 nmol/l or 32 μg/l. There was a very weak negative correlation between baseline 25-vitamin D levels and the degree of learning disability ($r=-0.14$). There was no significant difference between the four groups before treatment, however there was a clear trend of higher vitamin D levels with a significantly higher post treatment vitamin D level in the profound learning disability group compared to those mild deficiency. The average dose of vitamin D3 needed to increase the vitamin D level above 80 nmol/l was 1945 units daily. Our data shows that in a group of patients with significant risk factors of vitamin D deficiency, the average dose of vitamin D needed to correct deficiency was on average a modest dose given the need for anticonvulsants. Indeed the response to treatment was greatest in the group who had the most profound disability.

DOI: 10.1530/endoabs.37.EP310

EP311

Primary hyperparathyroidism presented as humeral brown tumor and multiple bone fractures

Lia Ferreira, Pedro Gomes, Pedro Cardoso, Vitor Valente, Ana Amado, Maria Teresa Pereira, Susana Garrido, Raquel Almeida, Cláudia Freitas, Cláudia Amaral, Isabel Palma & Fátima Borges
Centro Hospitalar do Porto, Porto, Portugal.

Primary hyperparathyroidism (PHPT) is frequently diagnosed as an incidental finding of hypercalcemia. Overt bone disease (osteitis fibrosa cystica or brown tumor), with history of pathologic fractures is a rare presentation.
A 48-year-old woman was admitted in with pain in the right thigh after a trivial fall. She also complained of generalized weakness and lethargy over the last 2 years. Her medical history mention multiple bone fractures in the last 6 years, namely left patella, both wrists and 4 years before surgery to lytic lesion of the right humerus, assumed as aneurysmal bone cyst. Her last follow-up CT, revealed recurrence of lytic lesion and she was propose to shoulder arthroplasty.
Plain X-rays and CTs revealed pathologic fracture of the right femur, multiple osteolytic lesions (right humerus, right femur, both shoulder blades and iliac bones), subperiosteal erosions in the distal phalanges and old fractures in the ribs. Bone scan showed increased uptakes over the right humerus, right femur and tibias. Femur fracture was managed with osteosynthesis and humeral biopsy documented multiple giant cells consistent with brown tumor of PHPT.
Analysis revealed severe PHPT (serum calcium 3.49 mmol/l, phosphorus 0.53 mmol/l, and PTH 1435 pg/ml). Ultrasound showed an $5.8\times3.9\times2.4$ cm mixed texture lesion in the left superior parathyroid and sestamibi scanning confirmed a left parathyroid adenoma, with a necrotic centre and bone uptakes coincident with previous bone scan.
Considering patient's age and high level of PTH, chest–abdomen CT were performed to excluded metastatic disease. Hereditary cancer syndromes were also excluded. Treatment was initiated with hydration and zolendronic acid and parathyroidectomy was perform. Histopathology confirmed the diagnosis of parathyroid adenoma. Hungry bone syndrome developed following surgery and was necessary treatment with calcium carbonate and alfacalcidol.
Conclusion
Pathological fractures in young adults should always be investigated. A high index of suspicion is necessary to diagnose this unusual presentation of PHPT.

DOI: 10.1530/endoabs.37.EP311

EP312

Comparative diagnostic value of ultrasound, ultrasound-guided fine needle aspiration and sestamibi scintigraphy for the correct preoperative localisation of parathyroid adenomas

Stefan Bilz[1], Nathalie Rogowski-Lehmann[1], Ina Krull[1], Michael Brändle[1], Rene Oettli[3], Walter Kolb[2] & Thomas Clerici[2]
[1]Division of Endocrinology, Department of Internal Medicine, Kantonsspital, St Gallen, Switzerland; [2]Department of Surgery, Kantonsspital, St Gallen, Switzerland; [3]Division of Radiology and Nuclear Medicine, Kantonsspital, St Gallen, Switzerland.

Background
This study prospectively assessed the sensitivity and positive predictive value (PPV) of ultrasound (US), ultrasound-guided fine needle aspiration with PTH measurement in the needle washout (US-FNA) and sestamibi scintigraphy (SS) for the localisation of parathyroid adenomas in patients with primary hyperparathyroidism (pHPT) and features of uniglandular disease.
Methods
51 consecutive patients with pHPT referred for first time surgery with an open minimally invasive approach (OMIP) were included. US and US-FNA and double isotope scanning with 99mTc pertechnetate and 99mTc sestamibi were performed in all patients. A localisation procedure was considered correct if surgical removal of a parathyroid gland at this.
Results
The sensitivities for correctly identifying the localisation of a hyperfunctioning adenoma were 65% (SS), 91% (US) and 68% (US-FNA).The respective PPVs were 94% (SS), 89% (US) and 96% (US-FNA). US and SS were consistent in 64%. The majority of the inconsistent studies were attributable to false-negative SS (22%). In US negative cases or if the lesion identified by ultrasound is very small (<0.25 ml), the addition of scintigraphy allowed the correct preoperative location of an adenoma in 39%. 47% of small US lesions (<0.25 ml) were correctly classified by US-FNA. 96% of the patients were cured following first surgery and and unilateral approach was succesful in 84%.Hemorrhagic and/or fibrotic changes following US-FNA were detectable intraoperatively in 28% and complicated surgery in three cases.
Conclusion
Preoperative localisation with US, SS and US-FNA allows a minimal/unilateral surgical approach in 84% of the patients. Ultrasound is significantly more sensitive and accurate than SS and US-FNA, which have a high PPV. The performance of all localisation procedures decreases in parallel to adenoma size, with ultrasound still remaining most sensitive. US-FNA, although highly specific, is complicated by a relatively high rate of haemorrhagic and/or fibrotic changes in the biopsied adenoma and should be used cautiously.

DOI: 10.1530/endoabs.37.EP312

EP313

The effects of single high dose vs daily low dose oral cholecalciferol treatment on vitamin D levels and muscle strenght in posmenapousal women

Mahmut Apaydin[1], Asli Gencay Can[3], Seyfullah Kan[1], Selvihan Beysel[1], Taner Demirci[1], Mustafa Caliskan[1], Muhammed Kizilgul[1], Ozgur Ozcelik[1], Muyesser Sayki Arslan[1], Mustafa Ozbek[1], Erman Cakal[1] & Tuncay Delibasi[1,2]
[1]Department of Endocrinology and Metabolism, Diskapi Yildirim Beyazit Teaching and Research Hospital, Ankara, Turkey; [2]Department of Internal Medicine, School of Medicine (Kastamonu), Hacettepe University, Ankara, Turkey; [3]Department of Physical Medicine and Rehabilitation, Diskapi Yildirim Beyazit Teaching and Research Hospital, Ankara, Turkey.

Introduction
Vitamin D deficiency is a common health problem. Vitamin D supplements are used to improve vitamin D status. However, there are few data about what doses to give and how often to give. The aim of this study is to determine the effects of single high dose or daily low dose oral cholecalciferol (vitamin D_3) on vitamin D levels and muscle strenght.
Methods and design
60 healthy postmenouposal women who had serum vitamin D levels were <20 ng/ml were enrolled in the study in the winter and spring of 2013–2014. First group ($n=32$) was given daily oral doses of 800 IU vitamin D_3, second group ($n=28$) was given single oral dose of 300 000 IU vitamin D_3. Serum vitamin D levels and muscle strengths were measured at the beginnig, 4th and 12th weeks. Muscle strength tests were performed at 60°s with Biodex system 3 isokinetic dynamometer.
Results
The mean vitamin D levels of first and second group at the beginnig were 10.2 ± 4.4 ng/ml; 9.7 ± 4.4 ng/ml ($P=0.637$), respectively. Significant increase in vitamin D levels was measured in both two groups at 4 and 12 weeks after vitamin D_3 treatment. At 4th week the increase in single dose of vitamin D_3 group (16.9 ± 5.8 ng/ml) (35.9 ± 9.6 ng/ml) was significantly higher than the daily low dose oral vitamin D_3 group (35.9 ± 9.6) (16.9 ± 5.8 ng/ml) ($P=0.01$). At 12th week the increase in single dose of vitamin D3 group (19.8 ± 7.2 ng/ml) (23.4 ± 4.7 ng/ml) was significantly higher than the daily low dose oral vitamin D_3 group (23.4 ± 4.7) (19.8 ± 7.2 ng/ml) ($P=0.049$). Quadriceps muscle strength score increased significantly in daily group at 4th week ($P=0.038$). Hamstring muscle strength score increase significantly in daily group at 12th week ($P=0.037$).
Conclusion
Although daily administration routes are effective in muscle strength, single administration is more effective in increasing vitamin D levels.

DOI: 10.1530/endoabs.37.EP313

EP314

Idiopathic hypercalcaemia in pregnancy not due to PTHrP: suggestion for another pathomechanism by genetic defect of 24-hydroxylase

Csaba Horvath[1], Szilvia Meszaros[1], Orsolya Acs[2], Eva Hosszu[2], Julia Nemeth[3], Emoke Csupor[4], Miklos Szathmari[1], Nandor Acs[5] & Eugene V McCloskey[6]
[1]1st Department of Internal Medicine, Semmelweis University, Budapest, Hungary; [2]2nd Department of Pediatrics, Semmelweis University, Budapest, Hungary; [3]Synlab Hungary, Budaors, Hungary; [4]Budavar Endocrine Center, Budapest, Hungary; [5]2nd Department of Obstetrics and Gynecology, Semmelweis University, Budapest, Hungary; [6]Centre for Metabolic Bone Diseases, Sheffield University, Sheffield, UK.

A 32-year-old women initially presented with recurrent kidney stones and was found to have nephrocalcinosis. She was found to normocalcaemic but hypercalciuric, with a plasma ionized calcium at upper-limit of normal and a PTH in lower normal range. One year later, during the first trimester of a pregnancy, she presented with severe hypercalcaemia, hypercalciuria and suppression of PTH. Extensive investigations for causes of hypercalcaemia excluded hyperparathyroidism, other endocrine diseases, hematologic or other malignancies, granuomatous diseases, renal tubular acidosis and milk-alkali syndrome. Plasma PTHrP was suppressed. She had not taken any form of vitamin D, however, her serum level of 25OHD3 was normal throughout the pregnancy (even in wintertime) and the serum level of 1,25(OH)2D was elevated. Continuous high oral and parenteral fluid intake resulted in a moderate decrease of hypercalcaemia and no change in hypercalciuria. At 35 weeks a healthy boy was born with a transient hypercalcaemia that normalized spontaneously within a few days. The maternal hypercalcaemia decreased but remained above reference range with continuing suppression of PTH. Disturbed vitamin D metabolism, especially a reduction in 24-hydroxylation by genetic mutations has been observed in familial cases of nephrocalcinosis and in infants with idiopathic hypercalcaemia after usual doses of vitamin D supplementation. We hypothesise that our patient had an insufficient 24-hydroxylation in the kidney and it has been intensified during pregnancy by the placenta as a well-known site of vitamin D activation for local immune purposes. If this is the case, then our patient could be the first one in whom the defective 24-hydroxylation produces hypercalcaemia without provocative effect of external vitamin D stimulation. To prove this hypothesis, the genetic analysis of mutations in CYP24A1 gene will be performed.

DOI: 10.1530/endoabs.37.EP314

EP315

The peripheral serotonin, the serum osteocalcin and CrossLaps: the assay in menopausal women

Mara Carsote[1,2], Cristina Capatina[1,2], Andra Caragheorgheopol[2], Dan Peretianu[3], Dana Manda[2], Rene Baloescu[2], Ana Maria Stefanescu[2], Diana Paun[1,2] & Catalina Poiana[1,2]
[1]C.Davila University of Medicine and Pharmacy, Bucharest, Romania; [2]C.I.Parhon National Institute of Endocrinology, Bucharest, Romania; [3]SCM Povernei Medical Centre, Bucharest, Romania.

Introduction
17th European Congress of Endocrinology 2015. The skeleton health is reflected by the turnover markers as serum CrossLaps (CL = bone resorption), and serum osteocalcin (OC = bone formation), and by the calcium metabolism parameters (as ionic blood calcium, and, probably, by the 24-h urinary calcium = 24-h ca). The peripheral serotonin might have intra-normal levels in patients with osteoporosis but yet represents a part of the complex equation related to the bone homeostasis.
Aim
we analysed the bone parameters, including serotonin in relationship to the bone loss as reflected by central DXA.
Material and method
This is a transversal study in menopausal women, starting from 2009 up to the present. No patient with active neoplasia or with tumours history (including primary hyperparathyroidism) was included. The patients with osteoporosis or anti-resorptive therapy for osteoporosis were also excluded. The lumbar DXA (Prodigy) provided the bone mineral density (BMD), and the WHO criteria allowed the including the patients into the osteopenia or the normal group. The blood assay were ionic calcium, OC, CL (ELISA kit), serotonin (ELISA), parathormon (PTH), 25-hydroxy vitamin D or 25OHD, (chemiluminescence), the urinary assay was 24-h ca. Statistical significance (SS) was considered at $P < 0.05$.
Results
55 women had osteopenia ($N1 = 22$), and normal DXA ($N2 = 33$). The ionic calcium was not SS different between the two groups (4.02 vs 3.92 mg/dl, $P = 0.23$), neither PTH (42.6 vs 44.6 pg/ml, $P = 0.5$), serotonin (155.36 vs 166.9 ng/ml, normal < 440 ng/ml, $P = 0.55$), 24-ur ca (0.14 vs 0.18 ng/ml, $P = 0.19$), 25OHD (14.64 vs 13.52 ng/ml, $P = 0.5$). BC, and OC are SS higher in osteopenia group vs normal: 0.49 vs 0.38 ng/ml ($P = 0.05$), respective 25.68 vs 17.73 ng/ml ($P < 0.005$).
Conclusion
Based on our observations, the bone turnover markers are higher in women with osteopenia vs normal, while the serotonin, or the calcium (regardless urinary or serum) and PTH are similar. Overall, a high prevalence of low 25-hydroxy vitamin D levels is found in menopause.

Disclosure
Part of these data is supported by C.Davila University of Medicine and Pharmacy, project no.33878/11.11.2014/Tineri cercetatori (Young Reserchers).
DOI: 10.1530/endoabs.37.EP315

EP316

Vitamin D deficiency in acutely ill patients

Ifigenia Kostoglou-Athanassiou[1], Eleni Pantazi[2], Iordanis Mavropoulos[2], Ourania Skioti[2], Georgios Katsoulis[2], Dimitrios Kousouris[3] & Socrates Kontogiannis[3]
[1]Department of Endocrinology, Red Cross Hospital, Athens, Greece; [2]2nd Department of Endocrinology, Alexandra Hospital, Athens, Greece; [3]Acute Care Unit, Department of Internal Medicine, Alexandra Hospital, Athens, Greece.

Introduction
Vitamin D deficiency has been reported to be widely found within the population. Vitamin D deficiency was also found to be prevalent in patients with autoimmune inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus. Vitamin D deficiency was reported in almost all patients with acute myocardial infarction in a US multicenter study. Low concentrations of 25-hydroxyvitamin D (25(OH)D) are reported to be an independent risk factor for cardiovascular events, in particular for strokes and sudden cardiac deaths.
Aim
The aim was to study and report vitamin D levels in acutely ill patients being cared for in an acute care unit.
Methods
In 20 patients being cared for in an acute care unit and in 20 controls matched for age and sex $25(OH)D_3$ levels were measured. In the patient population CRP and procalcitonin were also measured. $25(OH)D_3$ was measured by RIA, normal values being 47.7–114 nmol/l.
Results
In the patients being cared for in the acute care unit $25(OH)D_3$ levels were 30.33 ± 3.63 nmol/l (mean $\pm$ S.E.M.), whereas in the controls 60.37 ± 4.41 nmol/l ($P < 0.001$, Student's t-test). In the patients being cared for in the acute care unit vitamin D deficiency or insufficiency was found 18 of the 20 patients.
Conclusions
Low vitamin D levels were found in patients hospitalised in an acute care unit. These findings are in agreement with findings of other investigators having reported low levels of vitamin D in patients with acute myocardial infarction. It has been proposed that low vitamin D levels may be a risk factor for cardiovascular events and in patients with acute myocardial infarction may predict adverse outcomes. It has also been proposed that vitamin D levels may decrease during the acute phase response, however, more studies are needed to confirm or refute this hypothesis.

DOI: 10.1530/endoabs.37.EP316

EP317

The clinical profile of primary hyperparathyroidism: a single centre experience

Eleni Pantazi[1], Ifigenia Kostoglou-Athanassiou[2], Iordanis Mavropoulos[1], Ourania Skioti[1], Georgios Katsoulis[1] & Eleni Xanthakou[3]
[1]2nd Department of Endocrinology, Alexandra Hospital, Athens, Greece; [2]Department of Endocrinology, Red Cross Hospital, Athens, Greece; [3]Endocrinologist, Sparti, Greece.

Introduction
Primary hyperparathyroidism is currently a frequent disorder. In the past primary hyperparathyroidism was diagnosed late in the course of the disease. With the introduction of routine calcium measurements, as well as the awareness of the disease amongst clinicians, the disorder is frequently recognized in asymptomatic patients. Thus, the clinical profile of primary hyperparathyroidism is changing.
Aim
The aim was to describe the clinical profile of primary hyperparathyroidism in a single hospital center in Athens, Greece.
Methods
The clinical presentation and clinical characteristics of patients with primary hyperparathyroidism being followed up in a single center in Athens are described. All patients had a complete biochemical profile. In all patients calcium, PTH and

$25(OH)D_3$ were measured. In all patients thyroid and parathyroid ultrasonography was performed, as well as, parathyroid scintigraphy for the localisation of parathyroid tumors.
Results
In a single centre in Athens 35 patients with primary hyperparathyroidism are being cared for. Within this group of 35 patients, nine had mild primary hyperparathyroidism. Within this group of patients 12 were on treatment with cinacalcet for the management of the disease, whereas eight were on treatment with alendronate.
Conclusions
Primary hyperparathyroidism is a frequent disorder nowadays. As shown in the results of this study from a single center in Athens mild hyperparathyroidism is prevalent. Cinacalcet seems to be an option for patients not willing or not able to withstand surgery. Alendronate is another option for the pharmaceutical management of primary hyperparathyroidism, a drug treatment which aims to improve osteoporosis as well as calcium levels in patients with primary hyperparathyroidism.

DOI: 10.1530/endoabs.37.EP317

EP318

Raised calcium & PTH, not always a primary hyperparathyroidism

Fareeda Tabassum, Stephanie Baldeweg & Tom Kurzawinski
University College Hospital, London, UK.

Case
A 50-years-old gentleman underwent cardiac surgery which was complicated by postoperative arrythmias and ischemic stroke. He was found to have raised calcium of 2.9 (2.2–2.6 mmol/l) subsequent to which PTH was tested and found to be raised at 34.2 (1.6–6.9 pmol/l) which increased to 41.2 pmol/l in few days. He was referred for work up and management of primary hyperparathyroidism. An USS of the neck showed 1.5 cm nodule posterior to left thyroid lobe and Sestimibi scan also showed increased tracer uptake on the left side, findings consistent with parathyroid adenoma. During the course of investigations, calcium increased to 3.4 mmol/l and he required hospital admission for acute management of hypercalcaemia. In view of cardiac history and severe hypercalcaemia, he underwent left parathyroidectomy for parathyroid adenoma but histology of the excised gland showed features consistent with Parathyroid Adenocarcinoma. He was investigated to look for metastases. The CT scan of chest and SPECT CT did not show local or distant Metastases. A repeat surgery was undertaken for left hemithyroidectomy which showed no local spread of carcinoma. The calcium and PTH normalized after the surgery until 6 months when PTH increased again up to 11.4 pmol/l but it was found to be associated with hypocalcaemia and low Vitamin D and improved with Vitamin D replacement. He has been having regular follow up and being monitored with calcium and PTH. DEXA bone scan shows improving bone density. There has been no recurrence for 6 years after the surgery.
Discussion
Parathyroid carcinoma is a rare malignancy with incidence of $<1\%$ among all hyperparathyroidism cases. There are no distinguishing features or investigations to differentiate adenoma from carcinoma. It is mostly diagnosed on histological examination of the excised parathyroid gland. Raised PTH with hypercalcaemia is usually suggestive of primary hyperparathyroidism but severe hypercalcaemia with markedly raised PTH should raise suspicion of Parathyroid Carcinoma.

DOI: 10.1530/endoabs.37.EP318

Diabetes (pathiophysiology & epitemiology)

EP319

Insulin receptor substrate 1 and 2 genes polymorphisms are associated with metabolic syndrome but not cardiovascular risk factors in patients with metabolic syndrome

Fulden Sarac[1], Sefa Sarac[2], Sumru Savas[1] & Fehmi Akcicek[1]
[1]Department of Geriatrics Medicine, Izmir, Turkey; [2]Department of Cardiology, Izmir, Turkey.

Objective
The aim of our study was to investigate the relationships between insulin receptor substrat-1 (IRS-1) and insulin receptor substrat-2 (IRS-2) gene polymorphisms and cardiovascular factors such as blood pressures, BMI, LDL- cholesterol, triglyceride, HOMA-IR, homocysteine, hsCRP and fibrinogen levels in patients with metabolic syndrome (MetS).
Subjects and methods
The study population included 100 patients with MetS and 30 patients without MetS as control group. All entire coding exons of IRS-1 and IRS- 2 gene were amplified by PCR. Insulin resistance (IR) was estimated using the homeostasis model assessment (HOMA).
Results
In patients with MetS, 34 (34%) patients had G972R gene polymorphism and 66 (66%) had no nucleotide substitution at IRS-1 gene ($P<0.0001$). And, in IRS-2 gene, 44 (44%) had no nucletide substitution, 18 (18%) had G1057D heterozygous, 11 (11.0%) had G1057D homozygous, 2 (2%) had P1031P heterozygous/P1033PG1057 heterozygous, 17 (17.0%) had P1033P hererozygous, 3 (3.0%) had P1033P homozygous and 5 (5%) had P1033P heterozygous/G 1067D heterozygous polymorphisms in MetS ($P=0.0001$). However, all of control had no nucleotide substitution in IRS-1 and IRS-2 genes. There were no statistically differences between patients who had gene polymorphism and not polymorphism in IRS-1 and IRS-2 for systolic and diastolic blood pressures, BMI, LDL- cholesterol, triglyceride, HOMA-IR, homocysteine, hsCRP and fibrinogen.
Conclusion
Insulin receptor substrat 1 and 2 genes polymorphisms were associated with metabolic syndrome but not cardiovascular risk factors such as blood pressure, BMI, cholesterol, triglyceride, HOMA-IR, homocysteine, hsCRP and fibrinogen levels.

DOI: 10.1530/endoabs.37.EP319

EP320

Changing of expression of NOD-like receptors in GALT of rats at an experimental diabetes mellitus and pentoxifylline administration

Alex Kamyshny & Anna Degen
Zaporozhye State Medical University, Zaporozhye, Ukraine.

Introduction
Changing of expression of pattern-recognition receptors (PRR) of innate immune response by the gut-associated lymphoid tissue (GALT) can play a critical role in an induction and progression of T1DM.
Aim
To study the peculiarities of NOD2 receptors in gut-associated lymphoid tissues (GALT) of rats with experimental STZ-induced diabetes mellitus and pentoxifylline (PTX) administration.
Methods
Researches were made on Wistar rats. For an induction of diabetes streptozotocin was used in doses 50 mg/kg. Structure of population of NOD2+ cells has been studied by the analysis of serial histological sections using the method of indirect immunofluorescense with monoclonal antibodies to NOD2 of rat.
Results
It has been established that diabetes development was accompanied with 37–45% ($P<0.05$) increase in quantity of NOD2 cells on the 14th day, but by the 4th week of disease their number returned to the benchmarks. Induction of diabetes leads to increased in concentrations of NOD2 on 7–28% in macrophages and dendritic cells and a decrease on 8–12% in lymphocytes. PTX administration of diabetic animal reduces the quantity of NOD2+ cells on 29% ($P<0.05$) in mucous membrane of villus 42% in subepithelial zone of ILF by the 14th day of experimental diabetes mellitus. But by the 4th week of disease their number returned to the benchmarks in mucous membrane of villus and in subepithelial zone of ILF it increase on 29%. The concentration of NOD2 also decreased in 2nd week of diabetes on 8–15% in NOD2+-macrophages and NOD2+-dendritic cells.
Conclusions
The expression augmentation with NOD2 in ileum immunopositive cells can influence the differentiation of subsets of immunopositive cells and their proinflammatory cytokines production, thus acting as one of triggers of diabetes development and progression.

DOI: 10.1530/endoabs.37.EP320

EP321

Vitamin B12 levels and relationship between B12 and fasting insulin levels elderly patients with metabolic syndrome

Fulden Sarac[1], Sumru Savas[1], Sefa Sarac[2] & Fehmi Akcicek[1]
[1]Department of Geriatrics Medicine, Ege University Medical Faculty, Izmir, Turkey; [2]Department of Cardiology, Katip Celebi University, Atatürk Training and Research Hospital, Izmir, Turkey.

Introduction
Biochemical and clinical vitamin B12 deficiency has been demonstrated to be highly prevalent among patients with diabetes mellitus. The aims of the study were 1. to compare the vitamin B12 (VB12) levels, and 2. to investigate the relationship between VB12, fasting insulin and HOMA-IR levels in elderly patients with metabolic syndrome (MetS).
Subjects and method
Study population included 121 (mean age 64.3±14.1 years) (80 female, 41 male) elderly patients. Patients were evaluated for MetS by Adult Treatment Panel III (ATPIII). Data such as VB12, insulin and other tests were retrospectively searched. Vitamin B12 deficiency was defined as B12 concentrations <197 pg/ml.
Results
Metabolic syndrome was diagnosed in 39 elderly patients (%32.2). The prevalence of low VB12 was 45.8% in elderly with MS. Serum VB12 levels were significantly lower among patients aged ≥70 years ($P<0.05$). In elderly patients with MetS, mean levels of VB12, fasting insulin and HOMA were found to be 370.1±58.6 pg/ml, 13.4±1.1 μU/l, 3.0±0.1, respectively. However, mean levels of VB12, fasting insulin and HOMA were found to be 383.9±66.0 pg/ml, 8.4±2.7 μU/l, 2.71±0.9, in the other elderly patients, ($P=0.90$), ($P=0.70$), ($P=0.003$), respectively. Mean levels of VB12 were negatively correlated with fasting insulin levels ($r=-0.800$, $P=0.01$) in elderly with MetS.
Conclusion
Mean levels of VB12 were not different in elderly patients with or without MetS, but negatively correlated with fasting insulin in elderly with MetS.

DOI: 10.1530/endoabs.37.EP321

EP322

Does hepatitis C virus (HCV) infection has a role in the pathogenesis of diabetes mellitus in patients with β thalassemia

Vincenzo De Sanctis[2], Ashraf Soliman[1], Giancarlo Candini[3] & Heba Elsedfy[4]
[1]Hamad Medical Centre, Doha, Qatar; [2]Quisisana Hospital, Ferrara, Italy; [3]St Anna Hospital, Ferrara, Italy; [4]Ain Shams University, Cairo, Egypt.

Introduction
In patients with β thalassemia major (TM) The interplay between liver siderosis and hepatitis C virus (HCV) infection may facilitates the progression to insulin resistance (IR) and diabetes mellitus (DM).
Objectives
Many TM patients are infected with either HCV. Therefore, we aimed to explore if there is any association between DM and HCV-RNA positivity with different genotypes.
Patients and methods
148 TM patients (age range: 15–53 years; 72 males and 76 females), 78 were HCV-RNA positive. Fifteen patients (10.1%) had type 1 DM. The HCV genotype was done using specific primers in all thalassemic patients with DM as well as in 46 non diabetic TM patients. Serum HCV-RNA was detected using a sensitive polymerase chain reaction assay. We assessed also the frequency of DM in TM patients with HCV+ and HCV-RNA−, and HCV+ and HCV-RNA+.
Results
The commonest genotype in TM patients with and without DM was 1b (Table 1). HCV genotype did not differ statistically between diabetic and non-diabetic thalassemic patients (χ^2 test). In addition the frequency of DM did not differ among TM patients with HCV+ and HCV-RNA−, and HCV+ and HCV-RNA+. No significant correlation was observed between biochemical parameters (albumin, total protein, liver enzymes or INR) serum ferritin, IGF-I on the one hand and HCV-RNA status on the other hand.

Table 1.

HCV genotype	TM patients with diabetes	TM patients without diabetes
1b	9 (60%)	27(58.6%)
1b/2	0	1 (2.1%)
2	4 (26.6%)	14 (30.4%)
2a,2c	1 (6.6%)	1 (2.1%)
3a	1 (6.6%)	3 (6.5%)

Summary
Our study did not show statistically significant association between DM and HCV-RNA positivity. larger studies are required for acquiring better knowledge about the pathogenic mechanisms that link HCV infection with abnormal glycemic abnormalities.

DOI: 10.1530/endoabs.37.EP322

EP323

Abstract withdrawn.

DOI: 10.1530/endoabs.37.EP323

EP324

The relationship between higher left ventricular mass index and plasma total homocysteine levels in patients with type 2 diabetes mellitus

Harun Kundi[1], İhsan Ates[2], Nihal Ozkayar[3] & F Vasfi Ulusoy[1]
[1]Department of Cardiology, Ankara Numune Education and Research Hospital, Ankara, Turkey; [2]Department of Internal Medicine, Ankara Numune Education and Research Hospital, Ankara, Turkey; [3]Department of Nephrology, Ankara Numune Education and Research Hospital, Ankara, Turkey.

Purpose
The aim of the present study was left ventricular mass index (LVMI) in type 2 diabetes mellitus (T2DM) patients may be related increased circulating homocysteine (Hcy) levels.
Methods
The study group comprised 130 patients, and all patients were newly diagnosed with diabetes and were not taking any medication. Measures of left ventricular mass (LVM) were assessed using Devereux formula and left ventricular mass index (LVMI) was calculated as LVM divided by body surface area. Hcy levels were measured using high-performance liquid chromatography.
Results
Forty five patients (34.6%) of all patients with higher LVMI. In univariate logistic regression analyses age, creatinine and Hcy count all significantly associated with higher LVMI. When these three variables were included in a multivariate regression modeling Hcy levels were found to be significantly associated with the higher LVMI.
Conclusions
Hyperhomocysteinemia (Hhcy) can be a predictor of in T2DM patients.

DOI: 10.1530/endoabs.37.EP324

EP325

Description of practices related to insulin injection therapy and sharp disposal among patients attending the diabetic clinic, Colombo North Teaching Hospital, Sri Lanka

Kushani Atukorala[1,2], Deepama Sumanasekera[3], Kumudu Wickramasinghe[3] & Sumudu Wickramasinghe[4]
[1]Deptartment of Physiology, Faculty of Medicine, University of SriJayawardenapura, Gangodawila, Sri Lanka, [2]Deptartment of Family Medicine, University of Kelaniya, Kelaniya, Sri Lanka, [3]National Eye Hospital, Colombo, Sri Lanka, [4]MOH Office, Boralesgamuwa, Boralasgamuwa, Sri Lanka.

Introduction
Diabetic patients on insulin therapy are compelled to use sharps such as insulin needles and lancets on a regular basis. As a result thousands of used sharps and bloodstained materials are generated daily by them. While there is a huge concern over sharps disposal practices in healthcare settings, the sharps disposal practices of diabetic patients living at home has been poorly documented.

Methodology
Randomly selected sample of 158 diabetic patients were obtained from the diabetic clinic, Colombo North Teaching Hospital. Data collected using an interviewer administered questionnaire and clinic records.
Results
Sample population was aged between 21 and 90. Mean age 60. Majority had used insulin for more than 1 year 131/158 (83%). Very few 5/158 (3%) used the insulin pen while majority used syringes to inject insulin. Only 10 (6%) regularly checked blood sugar using needles/lancets. Majority 132/158 (84%) injected insulin more than twice per day and $\geq$50% used the same needle more than six times, for more than 3 days. Majority 150/153 (98%) of the syringe users recapped the needle. A significant number 73/158 (46%) also involved others when injecting and disposing needles. Used needles/pens were disposed in to a common household garbage bin, sharps container, toilet pit, garbage dump and indiscriminately by 66 (42%), 9 (6%), 8 (5%), 14 (8%), 11 (7%), respectively. Some 15/158 (9.5%) have collected sharps since beginning without disposing. Many respondents had received no information on how to dispose of their sharps. Those who recalled receiving information were more likely to dispose of their sharps safely.
Conclusions
Insulin-dependent diabetic patients are not educated on safe sharps disposal methods, leading to unsafe disposal of needles. Appropriate education on the correct disposal of sharps should be an integral part of their diabetic counselling.

DOI: 10.1530/endoabs.37.EP325

EP326

Vaccination status and factors affecting vaccination among diabetics

Kevser Onbasi[1], Bengur Taskiran[2], Lezan Keskin[3], Turkan Pasali Kilit[1] & Serdar Ucgun[1]
[1]Dumlupinar University, Kutahya, Turkey; [2]Yunus Emre State Hospital, Eskisehir, Turkey; [3]Malatya State Hospital, Malatya, Turkey.

Vaccines are the most effective tools for preventing some infections. World Health Organization (WHO) and Ministry of Health (MoH) in Turkey recommends vaccination for people with diabetes. Our aim was to determine the prevalence of vaccination rates among diabetes in three different cities (Kütahya, Eskisehir and Malatya) in Turkey. 475 patients (307 female, 168 male) attending outpatient clinics for endocrinology were asked to fill in a questionnaire. The vaccination rates were very low. The rate being vaccinated was 27% for influenza. The vaccination rate for pneumococcus, tetanus and hepatitis B were 8%, 20, 6% and 16, 2, respectively. The vaccination rates among type 1 diabetics were higher than type 2 diabetics. Survey results indicated that leading factor negatively influencing vaccine uptake for influenza was that 25.9% of diabetics did not know that they are in risk for influenza and 5.3% do not believe that there may be a threat of influenza pandemic or epidemic.6.1% did not want vaccination because of side effects. The reason for the lowest vaccination rate for pneumococcal vaccine may be dependent on the factor that this vaccine is not provided by health care providers, but the other vaccines are free for risk groups in Turkey. Also the pneumococcus vaccine is not well known among diabetics, because 60.6% of diabetics in our study population did not hear about the vaccine. 46.3% of diabetics reported that they did not know that there is a need of booster for tetanus immunization. Increased awareness of physicians may help improve vaccination rates against influenza, pneumococcal disease, tetanus and hepatitis B. Education programs for physicians and also diabetic patients may improve the vaccination rates in patients with diabetes.

DOI: 10.1530/endoabs.37.EP326

EP327

Prevalence of orthorexia in diabetic patients

Cuneyd Anil, Gozde Aritici, Hacer Ari & Neslihan Bascil Tutuncu
Baskent University Faculty of Medicine, Ankara, Turkey.

Introduction
Orthorexia (nervosa) is an eating disorder, characterised by an obsession with avoiding foods perceived to be unhealthy. Though it has not been recognised as a pathological entity in Diagnostic and Statistical Manual of Mental Disorders – IV yet, interest in the condition has increased recently. This study aimed to determine the prevalence and risk factors of orthorexia in a group of diabetic patients.
Methods and design
134 (63 female) diabetic patients who admitted to the outpatient clinic of our department were enrolled. Demographic information, educational status, diabetic history, care, and treatment, height, and weight of all cases were recorded. Ortho-15 Questionnaire was applied to all participants. Each patient can score minimum 15, maximum 60 points from this test. Those scoring 40 points and less are accepted to be orthorectic.
Results
The mean age of the group was 59.9 ± 11.7 years. The Ortho-15 test revealed that the minimum score was 25, and the maximum 46 points. No relation was determined between educational status, BMI and presence of orthorexia. 15.5% of males and 11.1% of females were found to be orthorectic ($P > 0.05$). The mean duration of diabetes of the whole group was 10.1 ± 8.8 years and there was no relation between duration of diabetes and presence of orthorexia.
Conclusion
This study revealed that orthorexia was not frequent in this group of patients. Performing the test on larger groups making comparisons, may introduce different results.

DOI: 10.1530/endoabs.37.EP327

EP328

Metabolic control in patients with 1 diabetes mellitus associated with depression

Yana Navmenova[1], Tatiana Mokhort[2], Elena Mahlina[3] & Maria Rusalenko[3]
[1]Gomel State Medical University, Gomel, Belarus; [2]Belarusian State Medical University, Minsk, Belarus; [3]The Republican Research Centre for Radiation Medicine and Human Ecology, Gomel, Belarus.

Objective
The assessment of glycemic control and concentration of lipids in the blood in patients with type 1 diabetes mellitus (DM-1), depending on the presence of depression (DP).
Methods
There were examined 163 patients with DM-1. To assess severity of DP there was used Hospital Anxiety and Depression Scale (HADS). There were determined the level of fasting blood glucose (BG), BG level in 2 hours after a meal, the average daily BG level for 3 days and HbA_{1C} level. Also there were determined the total amount of cholesterol (TC), triglycerides (TG), HDL cholesterol (HDL-C). The amount of LDL cholesterol (LDL-C) and the amount of very LDL cholesterol (VLDL-C) were determined by calculation.
Results
Increased level of HbA_{1C} was found in patients with DP, the mean daily glucose compared with patients without DP (9.70% vs 8.40%, $P < 0.001$; 9.02 mmol/l vs 8.10 mmol/l, $P = 0.03$ respectively). There has been established a positive correlative relationship between the level of DP according to the HADS scale and HbA_{1C} level ($r = 0.20$; $P < 0.05$), as well as between the level of DP according to the HADS scale and the level of the mean daily BG ($r = 0.22$; $P < 0.05$). Development of DP at DM-1 is associated with the level of HbA_{1C} 7.5% or more (OR = 0.89; $P = 0.03$; 95% CI 0.30–1.48). The results of evaluation of biochemical parameters characterizing lipid metabolism according to the presence of DP indicate, that the level of TC in patients with DP was higher than in patients without DP (5.10 mmol/l vs 4.80 mmol/l; $P = 0.04$). There has also been determined that the level of LDL-C was 3.10 mmol/l in patients with DP vs 2.65 mmol/l in patients without DP and exceeded by 14.5% the value of comparison group ($P = 0.05$).
Conclusions
The risk of development of DP in DM-1 is associated with decompensation of carbohydrate metabolism and dyslipidaemia.

DOI: 10.1530/endoabs.37.EP328

EP329

Trends in diabetic ketoacidosis presentations at a major rural referral centre in Australia

Tamara Young
Orange Health Service, Orange, NSW, Australia.

Aim
To study trends in presentation and management of diabetic ketoacidosis (DKA) at a rural referral centre, to ultimately assist with development of a formal management protocol.

Methods
A retrospective audit of medical records for all presentations of DKA over a two year period was conducted to source age of patient, distance from Orange Health Service, new onset vs known type 1 diabetes mellitus, initial pH, time to normalisation of ketones, any episodes of hypokalaemia or clinically significant hypotension during their management, episodes of hyperchloraemia, and overall length of stay. Statistical analysis was carried out to determine the mean and S.D., where data was normally distributed, and the median when data was not normally distributed. Furthermore, Spearman's correlations were conducted to examine the relationship between distance and age, length of stay and initial pH.
Results
23 cases met the inclusion criteria for analysis. The mean age of patients was 25 years. (S.D. 8.1 years). The mean length of stay was 4.57 days (S.D. of 3.34 days). Complications were recorded in half of patients with complete data sets. The mean initial pH was 7.134 with a S.D. of 0.144. There was a statistically significant positive association between age and length of stay ($rs=0.44$, $n=23$, $P<0.05$) and a statistically significant negative association between length of stay and initial pH ($rs=-0.51$, $n=23$, $P<0.05$). Distance was not correlated with length of stay nor initial pH.
Conclusions
A significant proportion of patients have a severe presentation, and many patients are transferred from outlying facilities. These factors need to be considered when planning service delivery and have been considered when developing a formal protocol appropriate for a major rural referral centre.

DOI: 10.1530/endoabs.37.EP329

EP330

Clinical characteristics in patients with type 2 diabetes mellitus: a cohort study

Sandra Herranz Antolín, Visitación Álvarez de Frutos, Ascensión Sutil Folgado, Dolores Mateo Pascual & Eduardo Platero Rodrigo
Hospital Universitario de Guadalajara, Guadalajara, Spain.

Objective
To assess metabolic control, cardiovascular risk factors and treatments in type 2 diabetes mellitus (T2DM) patients.
Methods
Observational and cross-sectional study of 238 T2DM patients who visited endocrinology clinics for the first time or those who did not undergo periodic revisions during the previous year of the study. All reported patients were outpatients, over 18 years of age and they signed informed consent statistical analysis was done by SPSS 20.0.
Results
61.8% males; main age. 64.2 ± 12.7 years. Diabetes duration (years): <1 8.8%; 1–5 20.2%; 5–10 25.2%; >10 45.8%. Cardiovascular risk factors: hypertension 80.7%, dyslipidaemia 80.3%, smoking 18.9% and obesity 61.4% (BMI 33.4 ± 8.2 kg/m^2).

Table 1.

	Mean ± S.D.	Targets (ADA 2013)	% patients who achieved targets
HbA1c (%)	8.1 ± 1.9	≤7	37.3
LDL-c (mg/dl)	109.6 ± 43.0	≤100	44.8
HDL-c (mg/dl)	42.3 ± 10.9	≥50	21.7
Triglycerides (mg/dl)	169.2 ± 116.0	≤150	53.4
Systolic BP (mmHg)	140.1 ± 21.6	≤130	36.3
Dystolic BP (mmHg)	77.4 ± 12.7	≤80	64.5

No patients achieved all the targets.

30.3 and 24.7% of the patients have not HbA1c and lipids tests respectively during the 6 previous months. Hypoglycaemic agents: patients with and without treatment: 91.6 and 8.4% respectively. Oral therapy 58.6%; oral theraphy + insulin 21.2%; insulin 12.2%. Antihypertensive drugs 74.8%; lipid lowering drugs 64.3%; antiplatelet agents 41.1%.

Conclusion
The prevalence of risk factors was very high in our study. However, no patients achieved all ADA targets, in spite of the wide use of antihypertensive, lipid lowering and hypoglycaemic drugs.

DOI: 10.1530/endoabs.37.EP330

EP331

The influence of actual and retroactive T2DM regulation on duration of hospital stay and clinical outcome of patients suffered from NSTEMI/STEMI

Zoran Gluvic[1], Pejka Kovacevic[2], Vladimir Samardzic[1], Jelena Tica Jevtic[1], Marina Vujovic[1], Vesna Popovic-Radinovic[1], Milena Lackovic[1], Bojan Mitrovic[1], Ratko Tomasevic[1], Anastasija Panic[3] & Esma R Isenovic[3,4]
[1]Zemun Clinical Hospital, Zemun, Belgrade, Serbia; [2]Bezanijska Kosa Hospital, Zemun, Belgrade, Serbia; [3]Laboratory for Molecular Genetics and Radiobiology, Institute for nuclear sciences 'Vinca', Belgrade, Serbia; [4]Albany College of Pharmacy and Health Sciences, The Pharmaceutical Research Institute at Albany, New York, New York, USA.

Introduction
A link between diabetes and coronary heart disease is well-known. The aim of this study is to examine the influence of actual and retroactive diabetes regulation parameters (admission glycaemia and HbA1C value) on duration of hospital stay and clinical outcome of T2DM patients suffered from NSTEMI/STEMI.
Material and methods
Cross sectional study involved 103 examinees with past history of T2DM actually hospitalised in CCU due to acute myocardial infarction (NSTEMI or STEMI). Beside some demographic, epidemiological, laboratory and clinical parameters, the impact of admission glycaemia (mmol/l) and HbA1C values (%) on duration of hospital stay and clinical outcome were observed. Obtained data were analysed by SPSS for Windows 18.0 statistical package. Level of statistical significance was 0.05.
Results
Out of 103 examinees, 66 (64.1%) suffer from STEMI. Mean age of study population is 67 ± 9 years, 59 (57%) are males. Mean T2DM duration is 7 (1–30) months and it influences on duration of hospital stay ($\rho=0.232$, $P<0.05$), but not on clinical outcome ($\rho=0.174$, $P>0.05$). Mean duration of hospital stay is 8 and 8.5 days in STEMI and NSTEMI patients respectively, with no difference between groups (log rank $\chi^2=0.476$, $P>0.05$). HbA1C values influence on duration of hospital stay ($\rho=0.213$, $P<0.05$), opposite to admission glycaemia ($\rho=0.148$, $P>0.05$). Out of four patients (3.9%), who passed away, three suffered from STEMI. Neither admission glycaemia ($\rho=0.165$, $P>0.05$) nor HbA1C values ($\rho=0.047$, $P>0.05$) do not have effect on clinical outcome.
Discussion and conclusion
In present study, admission glycaemia do not influence either on duration of hospital stay or clinical outcome. Diabetes duration and HbA1C values extend mean duration of hospital stay, but do not influence on clinical outcome.

DOI: 10.1530/endoabs.37.EP331

EP332

Serum apelin, salusin-α and salusin-β levels in type 2 diabetes mellitus and hypertension

Kader Ugur[1], Süleyman Aydin[2], Selçuk Yusuf Sener[1], Kadriye Yildirim[3] & Yusuf Özkan[1]
[1]Department of Endocrinology, Firat University Faculty of Medicine, Elazig, Turkey; [2]Department of Biochemistry, Firat University Faculty of Medicine, Elazig, Turkey; [3]Department of Internal Medicine, Firat University Faculty of Medicine, Elazig, Turkey.

Introduction
Diabetes mellitus (DM) is a metabolic illness caused by insulin resistance or lack of it. Hypertension (HT) has been seen frequently in diabetic patients, and causes morbidity and mortality with its complications. Salusins are vasodilator and hypotensive peptids which function most in cardiovascular system. Apelin is an insulin-sensitive, vasoconstructive, positive inotropic-effective peptide. In this study, determining the levels of serum salusin-α, salusin-β and apelin in diabetic and hypertensive patients as well as examining the relationship between diabetes mellitus and hypertension are aimed.

Methods
For this study, 36 patients with only diabetes, 41 patients with diabetes + hypertension, 32 patients with only hypertension, and 30 healthy controlled group are examined. In addition to regular blood tests, the levels of salusin-α, salusin-β, and apelin are also examined.
Results
The level of salusin-α was high in controlled group compared with HT and DM + HT groups (respectively, $P<0.05$, $P<0.01$). Although this level was high in DM group, it was not statistically significant. Compared with the control group salusin-β level was high in all groups, but it was not statistically significant ($P=0.205$). Compared with the control group, apelin level was low in DM group ($P<0.05$) but high in HT group, but not statistically significant. In DM + HT group, apelin level was similar as the control group.
Conclusion
As a result, salusin-α and salusin-β levels were observed to have increased in HT and DM + HT groups. The reason why these peptides increase is to decrease the arterial pressure. This may be a reply fort the cardioprotectivity. The reason why apelin level was low only in DM group may be due to fact that insulin level was low in diabetic group and apelin was an important mediator of glucose.

DOI: 10.1530/endoabs.37.EP332

EP333

Variability of anthropometric, echocardiographic and biochemical indices with comorbidity pathology – essential hypertension and type 2 diabetes

A S Shalimova[1], A N Belovol[2], M N Kochueva[1], V L Lutsyk[3] & A V Linskaya[3]
[1]Kharkiv Medical Academy of Postgraduate Education, Kharkiv, Ukraine; [2]Kharkiv National Medical University, Kharkiv, Ukraine; [3]Institute of Neurology, Psychiatry and Narcology of NAMS of Ukraine, Kharkiv, Ukraine.

The mechanisms of development and progression of essential hypertension (EH) and concomitant type 2 diabetes (DM2) still remain not completely studied, so the comprehensive evaluation of the contribution of various indicators to the formation of this comorbidity have scientific interest.
The aim of the study was comprehensive assessment of the variability of anthropometric, echocardiographic and biochemical parameters in patients with EH and concomitant DM2. We examined 243 patients aged 45–60 years. The main group consisted of 153 patients with EH stage II, grade 2 and DM2 moderate, subcompensated; comparison group – 70 patients with EH stage II, grade 2 without DM2. The control group consisted of 20 healthy individuals.
Integrated data processing was carried out with the help of factor analysis using principal component. In the analysis there were 73 variables, based on the relationships among which there were four factors that together explain 52.61% of the total variability of the empirical data. In this case the first and the most powerful factor explained 33.07% of the total variability of indices. The highest load of Factor 1 were at indicators diene conjugates, malondialdehyde, tumor necrosis factor-α, interleukin-6, blood glucose, insulin, HbA1c, HOMA, leptin, intima-media thickness of the common carotid artery, while at the negative pole of this factor were superoxide dismutase, catalase, endothelium-dependent vasodilatation, adiponectin, HDL).
Averaged factor estimates for Factor 1 were: 0.517 ± 0.025 – in the main group, -0.986 ± 0.039 – in the comparison group and -2.476 ± 0.037 – in the control group with highly significant differences between the factor scores in all groups ($P<0.001$).
Conclusion
We discovered four main factors, the general action of which explained 52.61% of variability indices in comorbid pathology – EH and DM2. Factor assessment of the most powerful Factor 1 with high significance made the studied groups of patients differ from each other.

DOI: 10.1530/endoabs.37.EP333

EP334

Salt addition and the risk of type 2 diabetes mellitus: a case–control study

Lina Radzeviciene[1], Rytas Ostrauskas[1] & Evelina Praneviciene[2]
[1]Institute of Endocrinology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania; [2]Faculty of Medicine, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania.

Introduction
Type 2 diabetes appears to involve interaction between susceptible genetic backgrounds and environmental factors. It is important to identify modifiable risk factors that may help reduce the risk of type 2 diabetes. Data on salt intake and the risk of type 2 diabetes are limited. The aim of the study was to assess the relationship between adding salt to prepared meal and the risk of type 2 diabetes mellitus.
Methods
A case–control study included 234 cases with a newly confirmed diagnosis of type 2 diabetes mellitus during the one whole year and 468 controls which were free of the disease. Cases and controls (ratio 1:2) were matched by gender and age (±5 years). A specifically designed questionnaire was used to collect information on possible risk factors of type 2 diabetes. Anthropometrical measurements were made according to World Health Organization recommendations. The odds ratios (OR), and 95% CI for type 2 diabetes were calculated by a conditional logistic regression.
Results
The cases had higher BMI and significantly lower education level, compared to the controls. Variables such as family history of diabetes, education, BMI, waist circumference, morning exercise, eating speed, cigarette smoking, arterial hypertension, plasma triglycerides, occupational and marital statuses were retained in the models as confounders because their inclusion changed the value of the OR by more than 5% in any exposure category. After adjusting for possible confounders about two-fold increased risk of type 2 diabetes mellitus was determined in those subjects whose adding salt to prepared meal when it is not enough or almost every time without tasting (1.82; 95% CI 1.19–2.78; $P=0.006$) vs subjects whose never adding salt to prepared meal.
Conclusion
Our data support a possible relationship between adding salt to prepared meal and the increased risk of type 2 diabetes mellitus.

DOI: 10.1530/endoabs.37.EP334

EP335

Relationship between adiponectin and anthropometric parameters, insulin resistance and transaminase levels in patients with nonalcoholic fatty liver disease and type 2 diabetes

Larysa Zhuravlyova & Anna Zhuravlyova
Kharkiv National Medical University, Kharkiv, Ukraine.

The basis of the pathogenesis of nonalcoholic fatty liver disease (NAFLD) is insulin resistance (IR) which appears on the background of abdominal obesity (AO) which, in turn, is a key factor in the emergence of an imbalance between adipocytokines entailing a disturbance of lipid and carbohydrate metabolism, which ultimately leads to the damage of the liver cells, the development of inflammation, fibrosis and apoptosis. The goal – to study features of changes in the level of adiponectin (AN), depending on the function of the liver and IR index in patients with NAFLD and type 2 diabetes mellitus (T2DM) and AO.
Methods
25 patients with NAFLD and T2DM (HbA1c $<7.5\%$) and control group ($n=10$) underwent clinical examination including assessment of BMI, waist circumference (WC), liver function (transaminases – ALT, AST) and index HOMA-IR.
Results
The changes in BMI were observed in 94.5% of patients, including obesity 1st degree – in 54.6%, 2nd degree – in 31.4 and 4.6% – obesity 3rd degree. AN level was reduced compared to control (8.7 ± 2.4 ng/ml vs 15.4 ± 2.1 ng/ml, $P<0.05$) and correlated with the degree of obesity – 6.5 ± 2.1 ng/ml in patients with grade 3 obesity ($P<0.05$). There was a negative relationship between the level of AN and BMI ($r=-0.36$; $P<0.01$), WC ($r=-0.34$; $P<0.05$). The level of AN significantly decreased with increasing levels of ALT ($r=-0.44$, $P<0.001$) and AST ($r=-0.46$; $P<0.001$). An inverse relationship between the level of AN and the index HOMA-IR was determined ($r=-0.46$; $P<0.001$).
Conclusions
Hypoadiponektinaemia in patients with NAFLD and T2DM is associated with AO, the deterioration of the liver function and progression of IR that contributes to the further development of metabolic abnormalities in the liver.

DOI: 10.1530/endoabs.37.EP335

EP336

Diabetic gallbladder, dyspepsia and metabolic effects

Larysa Zhuravlyova, Tetyana Moiseyenko & Maryna Filonenko
Kharkiv National Medical University, Kharkiv, Ukraine.

The purpose of the study was to determine the functional state of the gallbladder (GB) in patients with type 2 diabetes mellitus (T2DM) in combination with metabolic syndrome (MS).

Methods

40 patients with T2DM and obesity of I–II degree were examined as well as 20 healthy volunteers. Ultrasonography, dynamic echocholecystography and duodenal intubation were performed. The motor function of GB was assessed by emptying coefficient (Kempt $=(V_c)/V_0 \times 100\%$) and the index of contractility ($IC = V_{max}/V_{min}$). Lipid and carbohydrate metabolism was assessed.

Results

The following signs of GB hypotension were revealed: increase of GB initial volume to 80.2 ± 1.1 cm^3 (in the control group – 25.9 ± 1.9 cm^3) ($P < 0.05$); increase of GB hypokinesia – reduced Kempt of GB on 30th minute of investigation (0.6 ± 0.1 vs 49.2 ± 2.5 ($P < 0.05$)), on 45th minute (7.8 ± 0.3 vs 61.2 ± 2.7 ($P < 0.05$)) and on 60th minute (17.2 ± 0.4 vs 67.4 ± 2.4 ($P < 0.05$)). The reduction of GB propulsive function was confirmed by the increase of GB final volume to 66.3 ± 0.9 cm^3 vs 8.1 ± 0.8 cm^3, increase of the GB latent period duration to 28.2 ± 0.2 min vs 12.6 ± 0.5 min and reduced IC to 1.21 ± 0.1 vs 3.1 ± 0.3 ($P < 0.05$). Hypotonic-hypokinetic type of GB dyskinesia was confirmed by a reduction of GB wall thickness (2–3 mm) and a frequent presence of GB twist phenomenon. Typical clinical manifestations included dyspeptic signs, asthenic syndrome and silent course of the disease. The presence of dyskinesia in patients with T2DM and MS was accompanied by significant fluctuations of blood glucose levels during the day (the phenomenon of glycaemic swings), indicating the unsatisfactory state of carbohydrate control. Also, these patients showed signs of dyslipidaemia, which included increased content of TC, TG and LDL in comparison to control data.

Conclusions

Patients with T2DM and MS show signs of GB dyskinesia with dilatation and reduced GB contractile function that are associated with disorders of carbohydrate and lipid balance.

DOI: 10.1530/endoabs.37.EP336

EP337

Tumour necrosis factor-α and insulin resistance in patients with nonalcoholic fatty liver disease in combination with type 2 diabetes mellitus

Larysa Zhuravlyova & Olena Ogneva
Kharkiv National Medical University, Kharkiv, Ukraine.

Tumour necrosis factor-α (TNF-α) impairs liver function and contributes to the pathogenesis of nonalcoholic fatty liver disease (NAFLD) in patients with type 2 diabetes mellitus (DM-2) with different trophological status.

Purpose

To assess the relationship between the level of TNF-α and indices of carbohydrate metabolism in patients with NAFLD and its combination with DM-2 with different trophological status.

Methods

90 patients with isolated NAFLD and in combination with DM-2 with normal weight and obesity (BMI ≥ 30 kg/m^2) were divided into three groups: 1 group ($n = 20$) – comprized the patients with NAFLD, 2 group ($n = 20$) – patients with combination of NAFLD and DM-2 with normal body weight and 3 group ($n = 50$) – patients with comorbid disorder and obesity. The controls ($n = 20$) were apparently healthy individuals. The levels of insulin (IRI) and TNF-α were determined by ELISA method.

Results

TNF-α was significantly ($P < 0.001$) increased in all groups as compare to the control (24.2 ± 1.06 pkg/ml), the level was the highest in group 3 (96.6 ± 0.72 pkg/ml) and was significantly different from that in groups 1 and 2 (66.2 ± 1.07 pkg/ml and 86.4 ± 1.21 pkg/ml, respectively). In groups 1 and 2 the correlation was established between TNF-α and IRI ($r = 0.33$, $P < 0.05$ and $r = 0.37$; $P < 0.05$, respectively). In group 3 the significant correlation was established between the level of TNF-α and fasting blood glucose ($r = 0.46$; $P < 0.05$), IRI ($r = 0.78$; $P < 0.05$) and HOMA-IR ($r = 0.64$; $P < 0.05$).

Conclusion

The correlation between TNF-α and indices of carbohydrate metabolism is connected with the ability of TNF-α to enhance the carbohydrate metabolism, insulin resistance, and support the role of TNF-α in pathogenesis of NAFLD, namely, in damage of hepatic gluconeogenesis, especially in patients with associated DM-2 and obesity. In addition, isolated NAFLD can independently cause the metabolic consequences.

DOI: 10.1530/endoabs.37.EP337

EP338

Pancreatogenic diabetes

Seif eldin Yahia, Budd Mendis, Tom Crabtree & Nandini Seevaratnam
Nottingham University Hospital, Nottinghamshire, UK.

Aims

Diabetes mellitus secondary to pancreatic disease and pancreatic surgery (pancreatogenic; type 3c) is a discrete entity to common types of diabetes and there are no well established guidelines for its management. At Nottingham University Hospitals, we have set up a multidisciplinary pancreatogenic diabetes clinic since 2008. The aim of this study is to look at the outcome of the clinic since it's been established.

Methods

Case notes and hospital database of all 51 patients (32 male, 19 female) attending the clinic between 2008 and April 2014 were reviewed retrospectively. Their mean duration of diabetes was $5 + 0.76$ years.

Results

Mean HbA1c on first attendance was 70.4 (s.d. 21.6) and at 1 year it was 68.1 (s.d. 21.2). Mean weight at 1 year showed an increase from $75.2 + 3.1$ kg to $83 + 4.1$ kg. BMI increased from 26.0 to 29.8 kg/m^2. During the first year in the clinic, 15 patients had their medications reviewed and changed and there were only four patients admitted; three had problem with glycaemic control with DKA and one had multiple admissions due to hypoglycaemia.

Conclusions

There was improvement in HbA1c of the patients at 1 year. Mean BMI showed that patients were initially overweight and their BMIs have increased at 1 year. Attendance rates at the clinic are generally good; 80% of appointments have been attended. This showed that there is positive outcome of the pancreatogenic diabetes clinic. Therefore, patients with pancreatogenic diabetes should be managed in such clinic rather than usual diabetes clinics.

DOI: 10.1530/endoabs.37.EP338

EP339

Vitamin D level in impaired fasting glucose and impaired glucose tolerance (prediabetic) patients

Mehmet Gültekin[1], Zeliha Hekimsoy[2], Derya Öz[2], Ogün Hatiboglu[2], Pinar Alarslan[2], Bilgin Özmen[2], Ece Onur[3] & Ceyhun Gözükara[3]
[1]Department of Internal Medicine, Celal Bayar University Medical Faculty, Manisa, Turkey; [2]Division of Endocrinology and Metabolism, Department of Internal Medicine, Celal Bayar University Medical Faculty, Manisa, Turkey; [3]Department of Clinical Biochemistry, Celal Bayar University Medical Faculty, Manisa, Turkey.

Introduction

Impaired fasting glucose (IFG) is defined as being present in those whose fasting blood glucose level is consistently elevated above normal, but is not high enough to be considered as having diabetes mellitus. Impaired glucose tolerance (IGT) is defined as being present in those whose second hour plasma glucose level is higher than normal, but is not high enough to be considered as having diabetes mellitus. Low serum 25-hydroxyvitamin D levels are associated with glucose intolerance, diabetes mellitus, and metabolic syndrome. To date, the literature is conflicting regarding the relationship between vitamin D levels and prediabetes. Our aims in this study were to evaluate serum 25-hydroxyvitamin D levels and their association with prediabetic metabolic patterns.

Material and methods

Participants were 220 patients from our endocrine clinic: 85 with isolated IFG, 50 with isolated IGT, 85 with both IFG and IGT, and 80 normoglycaemic healthy subjects with similar age, gender, and BMI. A detailed history and physical examination of the patients were performed. 25-hydroxyvitamin D, calcium, phosphorus, albumin and PTH levels were measured. 25-hydroxyvitamin D levels were categorised as adequate if >30 ng/ml, insufficient if 20–30 ng/ml, and deficient if <20 ng/ml.

Results
We found significantly lower 25-hydroxyvitamin D levels in the IGT (11.7 ± 6.5 ng/ml) ($P < 0.007$) and IFG + IGT patients (13.2 ± 7.2 ng/ml) compared to controls (16.6 ± 9.8 ng/ml) ($P < 0.047$). Lower 25-hydroxy vitamin D levels were associated with a higher risk of IGT (OR 2.57, 95% CI 1.01–6.53, $P = 0.043$). 25-hydroxyvitamin D levels were similar in the control group and IFG group. Significant differences in 25-hydroxyvitamin D levels between the IFG group, IGT group and IFG + IGT group were not found.
Conclusion
Vitamin D insufficiency and deficiency are associated with IFG, IGT, and combined IFG and IGT. However, the only statistically significant association was that between 25-hydroxyvitamin D levels and IGT.
Disclosure
This work was supported by Celal Bayar University Research Foundation (grant number 2011-024).

DOI: 10.1530/endoabs.37.EP339

EP340

Effects of H. pylori eradication on metabolism and body weight in obese and non-obese patients

M Mar Roca-Rodríguez[1], Isabel Cornejo-Pareja[1], Leticia Coín-Aragüez[2], Juan Alcaide[2], Carlos Clu-Fernández[1], Laura Viñuela-González[3], Elena Durán-Martín[3], Laura Mora-Navas[3], Isabel Mancha-Doblas[1] & Francisco J Tinahones[1,2]
[1]Department of Endocrinology and Nutrition, Virgen de la Victoria and Regional Hospitals, Malaga, Spain; [2]Investigation Unit (IBIMA), Virgen de la Victoria Hospital, Malaga, Spain; [3]Department of Microbiology, Virgen de la Victoria Hospital, Malaga, Spain.

Introduction
Many studies showed that H. pylori infection could be an independent predictor for insulin resistance and could regulate metabolism and body weight.
Aim
To evaluate changes in metabolism induced by an oral glucose tolerance test (OGTT) before and after antibiotic eradication treatment in patients colonized by H. pylori.
Materials and method
Prospective case-controlled study with a sample of patients colonized by H. pylori. In an intra-subject analysis, clinical data and levels of ghrelin and GLP1 were analysed at baseline and post-OGTT before and after antibiotic eradication treatment.
Results
We studied 32 patients (75% women and 21.9% obese). Average age was 49 ± 11.5 and 46.9% had personal history of gastrointestinal disease. We found a significant decrease of HbA1c and 120 post OGTT glucose after treatment; and significant correlations between ghrelin with waist circumference and BMI (negative), and with glucose, insulin, HbA1c and LDL-Chol (positive). We also found significant positive correlations between GLP-1 and insulin, and between the difference in HbA1c and levels of GLP-1 post-treatment at all times after OGTT. No significant differences were found in obese patients before and after treatment, whereas non obese patients showed significant decrease in levels of 120 post OGTT glucose and HbA1c. Comparing non obese and obese patients, we found significant differences pre-treatment in fasting insulin and C-peptide; and post-treatment in diastolic blood pressure and C-reactive protein. 78.1% of patients completed correctly the treatment and 81.3% achieved the eradication of H. pylori.
Conclusions
Significant improvement in carbohydrate metabolism was observed after H. pylori eradication. No significant differences in body composition, blood pressure figures and levels of ghrelin and GLP-1 were found after treatment, but nearly significant decline in ghrelina. Significant correlations between plasma glucose and insulin with ghrelin and GLP-1 were found. More than 85% of patients achieve H. pylori eradication.

DOI: 10.1530/endoabs.37.EP340

EP341

Discrepancies between the glycosylated haemoglobin based criteria and glucose based criteria for diagnosis of diabetes and pre-diabetes

Sujan Sharma & Siddha Bahadur Rana Magar
Kathmandu University School of Medical Sciences, Dhulikhel, Nepal.

Objectives
The number of people with diabetes is increasing globally; hence necessitate identifying diabetes earlier and more efficiently. Recently, American Diabetes Association (ADA) recommended the use of glycated haemoglobin (HbA1c) as an alternative to glucose based criteria for diagnosing type 2 diabetes and pre-diabetes. Hence, we aimed to evaluate the discrepancies between HbA1c- and glucose-based criteria for diagnosis of diabetes and pre-diabetes in Nepalese population.
Methods
A total of 2502 subjects aged 30 years or older, who attended university hospital and subjected for measurement of HbA1c, fasting plasma glucose (FPG) and 2-hour plasma glucose (PPG) level were recruited in the study. Newly diagnosed diabetes and pre-diabetes were defined by ADA-glucose based and ADA- HbA1c criteria. Statistical analyses were performed using SPSS software to evaluate discripancies.
Results
The percentages of newly diagnosed individuals with diabetes were 12.87% (322/2502) using the FPG criterion alone, 12.07% (302/2502) using the PPG criterion alone, 14.55% (364/2502) using the HbA1c criterion alone and 10.51% (263/2502) using FFG, PPG & HbA1c criteria in combination. Significant discordance occurred for 3.28% (82/2502) with HbA1c- and glucose-based criteria and for 1.68% (42/2502) with HbA1c- and FPG-criteria. Among the study subjects, 2.86% of individuals with a FBG and 2.12% of individuals with HbA1c were found to be pre-diabetes.
Conclusions
Significant discordance exists between the HbA1c- and glucose-based diagnostic criteria for diagnosis of diabetes and pre-diabetes in Nepalese population. Hence, we concluded that using glucose based criteria merely may result in an underestimation of diabetes and pre-diabetes.

DOI: 10.1530/endoabs.37.EP341

EP342

Familial partial lipodystrophy linked to a novel peroxisome proliferator activator receptor-γ mutation, H449L

Tevfik Demir[1], Hüseyin Onay[2], David B Savage[3], Ayse Kubat Kuruuzum[4], Senay Savas Erdeve[5], Canan Altay[6], Samim Ozen[2], Leyla Demir[7], Umit Cavdar[1] & Baris Akinci[1]
[1]Division of Endocrinology, Dokuz Eylul University, Izmir, Turkey; [2]Department of Medical Genetics, Ege University, Izmir, Turkey; [3]Metabolic Research Laboratories, Wellcome Trust-Medical Research Council Institute of Metabolic Science, University of Cambridge, Cambridge, London, UK; [4]Division of Endocrinology, Istanbul University, Istanbul, Turkey; [5]Division of Pediatric Endocrinology, Dr Sami Ulus Women and Children's Hospital, Ankara, Turkey; [6]Department of Radiology, Dokuz Eylul University, Izmir, Turkey; [7]Department of Biochemistry, Ataturk Training Hospital, Izmir, Turkey.

Introduction
Familial partial lipodystrophy (FPL) is a rare genetic disorder characterised by a selective lack of subcutaneous fat that is associated with insulin resistance and diabetes. FPL has been reported to be caused by mutations in the peroxisome proliferator activator receptor-γ (PPARG) gene, which encodes a key transcription factor that regulates adipocyte differentiation and insulin sensitivity.
Material and methods
The objective of this study was i) to describe the phenotype associated with a novel heterozygous missense PPARG mutation, H449L, discovered in a Turkish family; and ii) to compare the fat distribution and metabolic characteristics of subjects with the PPARG H449L mutation ($n = 4$) to that of a cluster of FPL patients with various LMNA mutations ($n = 5$; R482W, R582H, L306V and T528M).
Results
Compared to patients with LMNA mutations, fat loss was generally less prominent in subjects with PPARG H449L mutation. Partial fat loss was limited to the extremities whilst truncal fat mass was preserved. The PPARG H449L mutation was associated with insulin resistance, hypertriglyceridemia and non-alcoholic fatty liver disease in all affected subjects but the severity was variable. Three of four mutation carriers were overtly diabetic or had impaired glucose tolerance. Pioglitazone therapy in these three individuals resulted in a modest improvement in their metabolic control, and regular menstrual cycles in both females.
Conclusion
We suggest that relatively modest fat loss in patients with PPARG mutations may render the recognition of the syndrome more difficult in routine clinical practice.

The PPARG H449L mutation is associated with insulin resistance and metabolic complications; however the severity is variable among the affected subjects, suggesting that additional factors such as variations in other predisposing genes, gender, age and lifestyle factors might affect the clinical features in patients with PPARG mutations.

DOI: 10.1530/endoabs.37.EP342

EP343

Irisin plasma level is connected with the android adipose tissue deposit

Katarzyna Pukajlo, Katarzyna Kolackov, Lukasz Laczmanski, Justyna Kuliczkowska-Plaksej, Marek Bolanowski, Andrzej Milewicz & Jacek Daroszewski
Department of Endocrinology, Diabetes and Isotope Therapy, Wroclaw Medical University, Wroclaw, Poland.

Irisin (Ir), a recently identified adipomyokine, cleaved and secreted to the circulation from the FNDC5 protein in response to physical activity and some environmental conditions has been postulated to induces the differentiation of a subset of white adipocytes into brown fat and mediates the beneficial effects of exercise on metabolic homeostasis. Polycystic ovary syndrome (PCOS) – one of the most frequent endocrinopathies affecting women of child-bearing age is associated with reproductive problems and also metabolic alterations leading to obesity and obesity-related diseases. It is commonly accepted that obesity-associated disorders are related to the type of fat distribution. Individuals with excess of visceral (android) fat but with normal BMI, called MONW (metabolically obese but normal weight), are burdened with obesity-related disease. The aim of our study was to evaluate the relationship between Ir plasma concentrations in PCOS patients and healthy control group in the context of adipose tissue deposits. Our study group consisted of 179 patients with PCOS and a population of 122 healthy control group (both groups aged 25–35 years). We isolated a MONW patients using DEXA criteria of depA (android fat deposit, $>30.2\%$ and BMI <25) for the Polish population. In the MONW patients we observed a negative correlation with Ir concentration. We found a statistically significant positive association between Ir concentration and type of adipose tissue deposit – (depA) in the whole study group ($P=0.006$) and in the control group ($P=0.00$), while in the PCOS a negative correlation between depA and Ir group ($P=0.00$) was shown. Our data revealed for the first time that Ir concentration is connected with type of body fat distribution. In this respect PCOS differs from healthy subjects. Moreover we confirmed that an increased Ir secretion in obesity could result from an adaptive response or Ir-resistance.

DOI: 10.1530/endoabs.37.EP343

EP344

The GH treatment results in the increase of irisin concentration in plasma

Beata Wikiera[2], Katarzyna Pukajlo[1], Lukasz Laczmanski[1], Natalia Sloka[1], Aleksander Basiak[2], Marek Bolanowski[1], Anna Noczynska[2] & Jacek Daroszewski[1]
[1]Department of Endocrinology, Diabetes and Isotope Therapy, Wroclaw Medical University, Wroclaw, Poland; [2]Department and Clinic of Endocrinology and Diabetology for Children and Adolescents, Wroclaw Medical University, Wroclaw, Poland.

Brown adipose tissue metabolism is of remarkable pathophysiological interest, because it could be a target for future therapies for obesity and metabolic syndrome. Irisin (Ir), recently identified novel adipomyokine is essential in a white-to-brown fatty tissue transdifferentiation, and mediates some of the positive influences on metabolic disorders through increase of energy expenditure. The exact regulation of Ir secretion and action is unknown but significant positive associations of circulating Ir with GHs and IGF1 were found. We studied Ir response in a group of patients treated with supraphysiological doses of GH (rGH). The study group consisted of 36 Turner syndrome (TS) patients aged 3.2–16.07 years (mean 8.2 years) diagnosed by karyotyping. The rGH was applied in a dose 0.05 mg/kg per day Prior to and following the treatment (mean 1.47 ± 0.89 years) anthropometrical data were recorded as well as biochemical parameters were measured: Ir, OGTT, insulin,IGF1, and IGFBP3. The increase of IGF1 concentration at the end of observation was significant (from 119.4 ± 62.46 to 413.37 ± 204.38 ng/ml, mean $\pm$ S.D., $P=0.000$). The significant rise of Ir level was recorded on rGH treatment (2.1 ± 1.03 vs 2.47 ± 0.79 μg/ml, mean $\pm$ S.D., $P=0.035$). The rGH treatment influenced insulin resistance revealed by increased HOMA values (median 0.64 ± 0.45 before and 0.92 ± 0.97 after, $P=0.02$). The correlation between Ir and IGF1 levels was not significant neither before nor on the treatment ($P=0.22$ and $P=0.95$ respectively). The correlation between Ir and insulin ($r=0.44$, $P=0.01$) and Ir and HOMA ($r=0.46$, $P=0.007$) was significant. Result of the study showed an increase in Ir level following GH application. It seems to be not IGF1 mediated. Ir may mediate some metabolic effects of GH treatment. We are unable to conclude whether Ir rise is connected with direct GH stimulation, their influence of body composition, or with altered insulin sensitivity.

DOI: 10.1530/endoabs.37.EP344

EP345

Acquired partial lipodystrophy is associated with increased risk for metabolic complications

Baris Akinci[1], Fatos Koseoglu[2], Huseyin Onay[3], Sevgi Yavuz[4], Canan Altay[5], Ilgin Yildirim Simsir[10], Secil Ozisik[1], Leyla Demir[6], Meltem Korkut[7], Nusret Yilmaz[8], Samim Ozen[3], Gulcin Akinci[9], Tahir Atik[3], Mehmet Calan[1], Mustafa Secil[5], Abdurrahman Comlekci[1] & Tevfik Demir[1]
[1]Division of Endocrinology, Dokuz Eylul University, Izmir, Turkey; [2]Department of Internal Medicine, Tepecik Training Hospital, Izmir, Turkey; [3]Department of Medical Genetics, Ege University, Izmir, Turkey; [4]Kanuni Sultan Suleyman Training Hospital, Izmir, Turkey; [5]Department of Radiology, Dokuz Eylul University, Izmir, Turkey; [6]Department of Biochemistry, Ataturk Training Hospital, Izmir, Turkey; [7]Division of Pediatric Gastroenterology, Yeditepe University, Istanbul, Turkey; [8]Division of Endocrinology, Akdeniz University, Antalya, Turkey; [9]Division of Pediatric Neurology, Dr. Behcet Uz Childrens' Hospital, Izmir, Turkey; [10]Division of Endocrinology, Ege University, Izmir, Turkey.

Objective
Acquired partial lipodystrophy (APL) is a rare disorder characterized by progressive selective fat loss. In previous studies, metabolic complications were reported to be relatively rare in APL, while they were quite common in other types of lipodystrophy syndromes. However, so far, there has been no systematic study on metabolic complications in APL.
Methods
We have systematically evaluated 21 APL patients in the Turkish Lipodystrophy Study Group (TuLip) registry who were enrolled in a prospective follow-up protocol. Patients with congenital generalized lipodystrophy (CGL), type 1 diabetes, type 2 diabetes and healthy controls were included for comparison. Subjects were investigated for metabolic abnormalities. Fat distribution was assessed by whole body MRI. Hepatic steatosis was evaluated by ultrasound, MRI and MR spectroscopy. Patients with diabetes underwent a mix meal stimulated C-peptide/insulin test to investigate pancreatic β cell functions. Leptin and adiponectin levels were measured.
Results
Fifteen individuals (71.4%) had at least one metabolic abnormality. Six patients (28.6%) had diabetes, 12 (57.1%) hypertrigylceridemia, 10 (47.6%) low HDL, and 11 (52.4%) hepatic steatosis. Steatohepatitis was further confirmed in two patients with liver biopsy. Anti GAD was negative in all APL patients with diabetes. Their leptin and adiponectin levels were decreased compared to patients with type 2 diabetes and controls. However, consistently very low leptin levels as detected in patients with CGL, was not the case. The mix meal test suggested that APL patients with diabetes had a significant amount of pancreatic β cells functioning, and their diabetes was apparently associated with insulin resistance.
Conclusions
Our results reveal that most patients with APL develop metabolic abnormalities associated with insulin resistance. Further research is needed to clarify if they would benefit from metreleptin treatment.

DOI: 10.1530/endoabs.37.EP345

EP346

Association between +276 G > T polymorphism of the adiponectin gene (*ADIPOQ*) and insulin resistance in Ukrainian patients with type 2 diabetes mellitus (T2DM)

Yuri Karachentsev, Nonna Kravchun, Maryanna Gorshunska, Lubov Atramentova, Nataliia Krasova, Tatyana Tyzhnenko, Zhanna Leshchenko, Alexander Gladkih, Artyom Pochernyaev, Yuliia Opaleiko, Olga Plohotnichenko & Victoria Poltorak
SI 'V. Danilevsky Institute of Endocrine Pathology Problems of NAMS of Ukraine', Kharkiv, Ukraine.

Variants of *ADIPOQ* have been inconsistently associated with adiponectin level in diverse populations. We explored association of single nucleotide polymorphism (*SNP*) in the *ADIPOQ* (*+276 G>T*, rs1501299) with circulating total adiponectin and insulin resistance (IR) in Ukrainian T2DM cohort.
Materials and methods
544 T2DM patients (M/F: 241/303, age 56.3±0.4 years, diabetes duration 7.8±1.0 years, BMI 31.7±0.2 kg/m^2, HbA1c 7.6±0.2%) and 215 healthy controls (C) were genotyped. The *SNP +276G>T* in the *ADIPOQ* was detected using PCR-RELP. Plasma total adiponectin, IR and lipid profile were determined. Statistical analysis was performed with ANOVA and χ^2 test.
Results
Comparing with C significant ($P<0.001$) increase in triglyceridaemia (2.89±0.12 vs 1.23±0.26 mM), plasma FFA levels (1.35±0.03 vs 0.34±0.07 mM), plasma insulin levels (132.47±6.11 vs 85.21±8.01 pM) and HOMA-IR (8.35±0.40 vs 1.77±0.41) as well as hypoadiponectinaemia (4.99±0.16 vs 11.80±1.45 mg/l) were observed in T2DM patients. Major allele in the studied groups was *G* (frequency in C: 0.691, and in diabetics: 0.601). In T2DM the *T* allele frequency was 0.399 and different significantly from C (0.307). In comparison with C, T2DM had more *TT* (16.9% vs 9.3%, $P<0.05$), but less *GG* (37.1% vs 47.4%, $P<0.05$) homozygotes. It was determined lower severity of dyslipidemia, i.e. total cholesterol ($P<0.01$), triglycerides ($P<0.02$) and β-lipoprotein cholesterol ($P<0.05$) against the background of less hypoadiponectinaemia (on 15.4%) in *GG* homozygotes ($P<0.1$) compared to *TT*-carriers. Higher HOMA-IR was revealed in *TT* compared to other genotypes with maximal difference in patients with obesity (HOMA-IR indexes in carriers of *TT*, *GT* and *GG* genotypes were 10.96±1.52, 8.40±0.65 and 8.96±0.74, respectively, $P<0.02$ for *TT* vs *GT* and *GG*).
Conclusions
The study demonstrates for the first time that *ADIPOQ* variants are associated with IR phenotype in Ukrainian T2DM patients. We suggest the predominant impact of metabolic disturbances and hyperinsulinaemia on diabetic hypoadiponectinaemia genesis.

DOI: 10.1530/endoabs.37.EP346

EP347

Vitamin D level in diabetic retinopathy

Rümeysa Selvinaz Erol[1], Muhammet Kazim Erol[2], Sayid Shafi Zuhur[3], Feyza Yener Ozturk[3], Esra Çil Şen[3], Aysegul Mavi[3], Masum Canat[3], Dilek Güven Çakmak[3] & Yüksel Altuntaş[3]
[1]Ordu Government Hospital, Ordu, Turkey; [2]Antalya Educational and Training Hospital, Antalya, Turkey; [3]Şişli Educational and Training Hospital, Istanbul, Turkey.

Purpose
To determine the relationship between grade of diabetic retinopathy and serum vitamin D levels in diabetic patients.
Materials and methods
A total of 173 diabetic patients consisting of patients without retinopathy ($n=67$), patients with non proliferative diabetic retinopathy (NPDRP group $n=47$), patients with proliferative diabetic retinopathy (PDRP group $n=59$) was included in the study. Age and sex matched 55 healthy subjects was taken as a control group. Patients with type 1 DM, those taking vitamin D, multivitamin including vitamin D, drug affecting vitamin D metabolism like rifampin, phenytoine was excluded from the study. Patients with chronic renal failure was also excluded. Dilated fundoscopic examination of all subject was done and serum creatinine, HbA1c, 25 hydroxy vitamin D (25 (OH) D) level of all subject were measured between May 2012 and September 2012.
Result
There was no statistical difference in age, sex, systolic tension, diastolic tension and BMI between groups. Serum creatinine level was also not statistically different between groups ($P=0.11$). The mean 25 (OH)D levels of PDRP group, NPDRP group, diabetic patients without retinopathy and control group was 11.9±6.4, 18.8±10.2, 16.6±7.5 and 20.1±9.2 ng/ml respectively. There was statistically significant difference between PDRP group and other groups in univariate analysis ($P<0.001$). When comparing 173 diabetic patients, regardless of retinopathy, with control group, 25 (OH) D levels was significantly lower in diabetic patients than control group ($P=0.004$).
Conclusion
Diabetic patients especially, patients with proliferative diabetic retinopathy had lower serum vitamin D level than healthy subjects. Additionally randomised, controlled, prospective studies are necessary to determine whether vitamin D treatment will stop or slow the progression of diabetic retinopathy in diabetic patients.

DOI: 10.1530/endoabs.37.EP347

EP348

Abnormalities in glucose metabolism are present in HCV/HIV co-infected patients with severe liver fibrosis even in the absence of diabetes

Manuel Cayón Blanco, Carolina García-Figueras Mateos, Gloria Baena Nieto, Patricia Bancalero Herrera, Salvador Pérez Cortés & Alberto Terrón Pernía
Hospital SAS Jerez de la Frontera, Jerez de la Frontera, Andalusia, Spain.

Rationale
Type 2 diabetes mellitus (T2DM) is a well known independent prognosis factor associated with cirrhosis. Nevertheless, few studies are focused on the association between glucose metabolism and liver fibrosis in HCV/HIV patients and their conclusions are contradictory. The aim of our study was to investigate the relationship between glucose homeostasis and liver fibrosis in these patients.
Methods
In a cross-sectional study, we compared prevalence of glucose disorders and data related to its homeostasis according to degree of liver fibrosis. Liver stiffness was measured using transient elastography. Severe liver fibrosis was defined as liver stiffness ≥14 kPa. Insulin resistance was defined as a level of homeostasis model for assessment (HOMA-IR) ≥2.
Results
65 HCV/HIV co-infected patients were included. Prevalence of prediabetes and T2DM was higher (40 and 24%, respectively) among patients with severe fibrosis as compared to 37 and 3.7% among those with less severe degree of fibrosis ($P=0.005$). Among parameters related to glucose metabolism, levels of fasting glucose, HbA1c and HOMA-IR were significantly higher in patients with severe fibrosis ($P=0.006$, $P=0.048$ and $P=0.001$ respectively). Also, there was a positive correlation between HOMA-IR and liver fibrosis ($r^2=0.5$; $P<0.001$). When patients with T2DM were excluded, levels of fasting plasma insulin, HOMA-IR and the prevalence of insulin-resistance, were significantly higher among those with severe fibrosis ($P=0.004$, $P=0.003$ and $P=0.049$, respectively) and the positive correlation between HOMA-IR and liver fibrosis remained significantly present ($r^2=0.45$; $P<0.001$).
Conclusions
Our data support that hyperinsulinism and insulin-resistance are frequently observed in HCV/HIV co-infected patients with severe liver fibrosis even in absence of overt T2DM. Detection of a high degree of liver fibrosis in HCV/HIV co-infected patients is another reason to optimize glycaemic control in this population.

DOI: 10.1530/endoabs.37.EP348

EP349

Gamma glutamyl transferase and C-reactive protein in type 2 Saudi diabetic patients in relation to management modality and components of metabolic syndrome

Suhad Bahijri[1], Maimoona Ahmed[1], Khalid Al-Shali[1], Samia Bokhari[1,3], Amani Alhozali[1], Anwar Borai[1,2], Amani Gusti[1,3], Ghada Ajab Noor[1], Jawahir Al Ahmadi[1], Ahmed Alghamdi[1], Mohammed Asiri[1], Osamah Bashawieh[1], Abeer Aljahdali[1] & Jaakko Tuomilehto[1,4]
[1]Saudi Diabetes Research Group, Faculty of Medicine, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia; [2]King Abdullah International Medical Research Center, King Saud bin Abdulaziz University for Health, Jeddah, Saudi Arabia; [3]King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia; [4]Department of Public Health, Hjelt Institute, University of Helsinki, Helsinki, Finland.

Background
Different management modalities are used to control hyperglycaemia associated with type 2 diabetes (T2DM). Research has indicated an association of single or combined insulin therapy with increased cardiovascular events. Metabolic syndrome (MS), as well as increased levels of C-reactive protein (CRP), and gamma glutamyl transferase (GGT) are also associated with increased CVD risk.
Aim
To study the relationship between management modality, glycaemic control, components of metabolic syndrome and serum levels of GGT and CRP.
Methods
T2DM subjects were recruited from outpatients clinics at two hospitals in Jeddah. Pregnant subjects, and those having any other severe chronic illness or diabetes complications were excluded. Anthropometric measurements, and blood pressure were taken. Treatment plan was recorded. Fasting blood samples were obtained to measure glucose, HbA1c, lipids profile, CRP and GGT.
Results
A total of 153 subjects were recruited (46.4% males, 53.6% females). MS was present in 131 (85.6%) patients. In spite of significantly lower mean HbA1c in hypoglycaemic drugs users compared to means in those using single or combined insulin therapy ($P<0.001$), and significantly lower mean diastolic blood pressure (DBP) in insulin users ($P=0.025$), no significant difference was found in means of GGT or CRP. Significantly higher mean GGT was found in uncontrolled compared to controlled, and hypertensive compared to normotensive patients ($P<0.05$ in both cases).GGT correlated positively with triglycerides ($r=0.227$, $P=0.028$), and negatively with HDL-C ($r=-0.188$, $P=0.049$). CRP correlated positively with waist circumference ($r=0.204$, $P=0.045$), and mean value being higher in abdominally obese group compared to non-obese ($P=0.048$).
Conclusions
Serum GGT and CRP levels do not appear to be affected by management regimen in T2DM Saudi patients. Some components of MS, hypertension and poor glycaemic control are associated with higher levels of either CRP or GGT, hence increased cardiovascular risk.

DOI: 10.1530/endoabs.37.EP349

EP350

The prevalence of metabolic syndrome in patients with diagnosed type 2 diabetes

Aldi Shehu[2], Erion Thengjilli[1], Albana Doko[1] & Florian Toti[1]
[1]University Hospital Center 'Mother Theresa', Tirana, Albania; [2]Laboratory 'Intermedica', Tirana, Albania.

Background and aims
The identification of metabolic syndrome (MS) is important for the appropriate management of associated cardiovascular risk factors. There are different criteria for the diagnosis of the metabolic syndrome proposed by the WHO and the National Cholesterol Education Program 2001 – NCEP/ATP III. The aim of our study was to determine the prevalence of the MS as the NCEP/ATP III criteria in a selected population of type 2 diabetes.
Patients and methods
We randomly selected 500 patients with T2 diabetes in Tirana district. 321/500 (64.2%) responded, 158 (49.2%) males. All the patients had completed anthropometric measures and lipid profile after an 8-h fast. The patients having two more criteria except diabetes, were defined as having MS.
Results
The prevalence of the MS was 64.5%, males 56.8% and females 75.7%. The prevalence increased with age, from 16% before 40 years of age to 78% at 70 years. Diabetes duration was not different in patients with or without MS (M: 6.7 ± 3.4 vs 6.9 ± 3.7; F: 7.2 ± 3.8 vs 6.8 ± 3.6 years). The number of components of the MS was related to the age (ANOVA $P<0.05$) but not to diabetes duration. Central obesity was present to males 36% females 85.4%, HTA 49.6 and 60.2%, low HDL 52 and 90%, high triglycerides 70.9 and 66.7% respectively. HbA1c was higher in persons with MS (9.6 ± 2.2 vs $8.7\pm1.4\%$, $P<0.01$).
Conclusion
The results show that MS is two-fold more prevalent in type 2 diabetes, compared with the general Albanian population (64.5 vs 32%). The levels of cardiovascular risk factors are increased in type 2 diabetics and urged immediate efforts directed at controlling the components of MS (mainly obesity, physical inactivity and lipid control).

DOI: 10.1530/endoabs.37.EP350

EP351

Insulin-induced lipohypertrophy diagnostics in diabetic patients: subcutaneous fat ultrasonography

Natalya Volkova, Ilya Davidenko, Julya Rudakova & Anna Sesukina
Rostov State Medical University, Rostov-on-Don, Russia.

Introduction
Lipohypertrophy (LH) is a chronic complication of diabetes mellitus that caused by frequent s.c. injections of insulin. Nowadays, LH were modified due to good quality modern insulin and expansion their concentration. As a result, some difficulties of diagnosis were appeared.
Design
The aim of this study has been to compare the frequency of insulin induced LH in diabetic patients revealed by ultrasonography of subcutaneous fat with those founded by palpatory method. This study was done on 215 diabetic patients (142 females and 73 males, mean age was 46 years) who had been under the treatment with insulin a mean 10 years. Observation and palpation techniques, as well as ultrasonography of subcutaneous fat were used in assessing LH in these diabetics. Evaluation of subcutaneous fat was made in typical injection sites: paraumbilical and buttocks regions, lateral surfaces of hips and shoulders. All patients injected insulin in physiological regimen.
Results
On the basis of palpation LH were revealed in 66 patients (30.7%), while pathologic areas of subcutaneous fat didn't discover in 149 subjects (69.3%). Further ultrasonography of injection sites was performed to all patients. LH were revealed in 186 patients (86.5%), including those 66 subjects with palpatory changes. Pathologic areas of subcutaneous fat the most often were occurred in paraumbilical regions – 131 patients (61%). Also LH were found simultaneously in two sites: paraumbilical regions and lateral surface of hips – 32 subjects (15%); paraumbilical regions and lateral surface of shoulders – 24 patients (11%).
Conclusions
LH were modified due to good quality modern insulin and expansion their concentration. As a result, pathologic areas of subcutaneous fat were revealed in 30.7% patients by palpation, while LH were found in 86.5% subjects by ultrasonography. Ultrasonography of subcutaneous fat could be used to diagnose LH in diabetic patients in clinical daily practice.

DOI: 10.1530/endoabs.37.EP351

EP352

Unvisible lipohypertrophy and diabetes compensation: is there link?

Natalya Volkova, Ilya Davidenko & Julya Rudakova
Rostov State Medical University, Rostov-on-Don, Russia.

Introduction
Lipohypertrophy (LH) is a chronic complication of diabetes mellitus that could develop in any age, any injection site, and be any size. At present time, new method, as ultrasonography of subcutaneous fat, of LH diagnostics were appeared.
Design
The aim of this study has been to estimate efficiency of insulinotherapy in diabetic patients after LH was diagnosed by ultrasonography. This study was done on 50 diabetic patients (31 females and 19 males) who had been under the treatment with insulin a mean 10 years. Ultrasonography of subcutaneous fat was used in assessing LH in typical injection sites. All patients injected insulin in physiological regimen. HbA1c level, fasting and postprandial glucose, episodes of hypoglycaemia, body mass and BMI were evaluated at the moment of LH and after 6 month in all patient. Results were considered to be statistically significant $P<0.05$.
Results
BMI reduced from 26.34 ± 6.07 kg/m^2 to 25.25 ± 4.06 kg/m^2 ($P<0.05$). Body mass decreased from 72.44 ± 15.75 kg to 70.08 ± 15.02 kg ($P<0.05$). Also good glycaemic control was demonstrated by measuring glucose and HbA1c level. Thus fasting glucose reduced from 9.03 ± 3.98 mmol/l to 7.11 ± 2.95 mmol/l ($P<0.05$). Postprandial glucose decreased from 10.27 ± 3.72 mmol/l to 9.34 ± 2.61 mmol/l ($P<0.05$). HbA1c level reduced from $9.27\pm2.32\%$ to $7.43\pm1.52\%$ ($P<0.05$). Frequency of hypoglycaemia reduced from 1.97 ± 2.23 to 1.10 ± 0.91 in month ($P<0.05$).

Conclusions
There were significant improvement of all estimated parameters which characterised the diabetes compensation after changing injected sites because of detected by ultrasonography LH. Since ultrasonography of subcutaneous fat is more sensitive than classic LH diagnostics, it might be used in general clinical practice instead of common detection of LH. Thus, early LH diagnostics can provide to good glycaemic control.

DOI: 10.1530/endoabs.37.EP352

EP353

Glycoregulation during pregnancy

Violeta Mladenovic[1], Aleksandar Djukic[1], Svetlana Djukic[1] & Djuro Macut[2]
[1]CC Kragujevac, Kragujevac, Serbia; [2]CC Serbia, Belgrade, Serbia.

Background
Pregnancy presents a state of insulin resistance that can predipose diabetes development in some women, and is associated with increased risk for neonate and for mother. Gestational diabetes is a period of glucose intolerance that manifests at the beginning of the third trimester.
Aim
The aim of this study is to analyse glycoregulation in healthy pregnant women.
Materials and methods
This study included 77 healthy pregnant women in third trimester registered in centre for endocrinology CC Kragujevac that were tested, according to positive 3 h OGTT with 100 g glucose (ADA Criteria), with specifying glycaemia and insulinaemia in 0, 60, 120, and 180 min, and HbA1c. According to OGTT results we divided patients in two groups: normal glucose tolerance (NGT) and gestational diabetes mellitus (GDM).
Results
Patients were average 30.8 ± 4.7 (19–41) years old. It was shown that there was impact the number of risk factors on degree of glucose tolerance disorder ($P = 0.034$), while most of patients had no risk factor (48%). The average glycaemia during OGTT in NTG vs GDM in 0 min was 3.92 ± 0.43 vs 4.39 ± 0.46 in 120 min, 6.34 ± 0.99 mmol/l vs 7.14 ± 1.4 mmol/l. From 77 patients, 18 was with GDM (23.3%). As pregnancy progress, disorder of glucose tolerance increased (in second and third trimesters), while 4 weeks after delivery all were with NGT. The average insulinaemia during pregnancy was the greater during third trimester in 0 and 60 min in GDM group, in NTG vs GDM in 0 min was 30.81 ± 14.81 vs 33.33 ± 16.29, while in 120 min was 198.1 ± 144.25 μIU/ml vs 200.77 ± 120.82 μIU/ml. The average HbA1c during pregnancy was: NTG vs GDM 5.06 ± 0.29% vs 5.1 ± 0.27%.
Conclusion
This research brought for the first time established values of glycaemia during OGTT in healthy women in our population during third trimester, and showed increased prevalence of GDM.

DOI: 10.1530/endoabs.37.EP353

EP354

Smoking habits and the risk of type 2 diabetes mellitus in women

Lina Radzeviciene[1], Rytas Ostrauskas[1] & Evelina Praneviciene[2]
[1]Institute of Endocrinology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania; [2]Faculty of Medicine, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania.

Introduction
Type 2 diabetes appears to involve interaction between susceptible genetic backgrounds and environmental factors. It's important to identify modifiable risk factors for type 2 diabetes, which may help reduce the risk of the disease. The aim of the study was to assess the relationship between smoking and the risk of type 2 diabetes in women.
Methods
In case–control study included 168 cases with a newly confirmed diagnosis of type 2 diabetes during the one whole year and 336 controls which were free of the disease. A specifically designed questionnaire was used to collect information on possible risk factors of type 2 diabetes. Smoking was assessed according to: smoking habits, duration of smoking, number of cigarettes smoked per day, pack years, and smoking cessation. The odds ratios (OR), 95% CIs for type 2 diabetes were calculated by a conditional logistic regression.
Results
The cases had higher BMI and significantly lower education level, compared to the controls. Variables such as family history of diabetes, education, BMI, waist circumference, morning exercise, eating speed, cigarette smoking, occupational and marital statuses were retained in the models as confounders because their inclusion changed the value of the OR by more than 5% in any exposure category. After adjustment for possible confounders increased risk of type 2 diabetes was determined for those, whose smoked ten and more cigarettes per day (OR = 2.83; 95% CI 1.04–7.71 vs non-smokers). It has also been defined an association between the disease and duration of smoking (OR = 4.55; 95% CI 1.11–18.61 for 40 years or more smokers vs non-smokers) and those, whose smoking cessation is 19 years and less had higher risk for diabetes (OR = 6.40; 95% CI 1.50–27.34 vs non-smokers).
Conclusion
Our data support a possible relationship between smoking and the increased risk of type 2 diabetes in women.

DOI: 10.1530/endoabs.37.EP354

EP355

Optimal glycaemic control and a low rate of micro and macrovascular complications in patients with HNF1A–MODY treated in a dedicated tertiary referral centre

Siobhán Bacon, Ma Peyh Kyithar, Ailbhe McCarthy, Marie Burke & Maria Byrne
Mater Misericordiae University Hospital, Eccles St, Dublin 7, Ireland.

Objective
HNF1A gene mutations are the most common cause of monogenic diabetes. Patients with HNF1A–MODY display sensitivity to sulphonylurea therapy, however the long term efficacy has yet to be established. There is also limited literature as to the prevalence of complications in this unique cohort. The aim of the study was to determine the natural progression of HNF1A–MODY diabetes in a dedicated MODY clinic.
Design
$n = 60$ HNF1A–MODY mutation carriers and a cohort of $n = 60$ BMI, age, ethnicity, and diabetes duration matched T1DM participated in the study. All subjects were phenotyped. Additional samples were drawn for the cardiovascular biomarkers sCD36/hsCRP. A 12 lead ECG was completed. Peripheral neuropathy and peripheral vascular disease was assessed clinically/ABI. Retinal screening was performed on an annual basis. Detailed clinical follow up of the HNF1A–MODY cohort occurred on a bi-annual basis for 84 months.
Results
Following a genetic diagnosis of MODY the majority of cohort remained insulin independent at 84 months follow up (75%). The HbA1c in the sulphonylurea treated group improved significantly over the study period (55 mmol/mol (45–64) vs 46 mmol/mol (39–58), $P = 0.009$). The group that remained on sulphonylurea therapy alone lost an average of 5.6 kg weight during the study follow up. The rate of retinopathy was significantly lower than that noted in the T1DM group (18.3% vs 50%, $P = 0.0001$). There was also a lower rate of microalbuminuria, neuropathy, and cardiovascular disease in the HNF1A–MODY group than that noted in the T1DM group.
Conclusions
This study demonstrates that the majority of HNF1A–MODY mutation carriers can be maintained successfully on sulphonylurea therapy in the long term. We note a significantly lower rate of micro- and macrovascular complications than that reported in the literature. The use of appropriate therapy at early stages of the disorder and attendance at a dedicated MODY clinic may decrease the rate of complications.
Disclosure
This study was supported by a grant from the Health Research Board of Ireland awarded to S Bacon. Grant number HPF-2013-459.

DOI: 10.1530/endoabs.37.EP355

EP356

Plasma omentin-1 level does not change in the first trimester in women with gestational diabetes mellitus

Seda Sancak[1], Hasan Aydın[2], Mehmet Sargın[3], Asuman Orçun[4], Ali Özdemir[5], Ayhan Çelik[6] & Gülgün Aslan[7]
[1]Division of Endocrinology and Metabolism, Fatih Sultan Mehmet Training and Educational Hospital, Istanbul, Turkey; [2]Division of Endocrinology and Metabolism, Yeditepe University Hospital, Istanbul, Turkey; [3]Diabetes Department, Kartal Lutfi Kirdar Training and Educational Hospital, Istanbul, Turkey; [4]Division of Biochemistry, Kartal Lutfi Kirdar Training and Educational Hospital, Istanbul, Turkey; [5]Department of Internal Medicine, Fatih Sultan Mehmet Training and Educational Hospital, Istanbul, Turkey; [6]Division of Obstetrics and Gynecology, Fatih Sultan Mehmet Training and Educational Hospital, Istanbul, Turkey; [7]Department of Internal Medicine, Kartal Lutfi Kirdar Training and Educational Hospital, Istanbul, Turkey.

Objective
Gestational diabetes mellitus (GDM) is strongly associated with maternal obesity. Omentin-1 is secreted from the adipose tissue and enhances insulin action. Circulating levels are inversely correlated with body weight, decreased in type 2 diabetes. Pre-existing maternal obesity has been shown to be associated with lower omentin-1 expression in placenta, adipose tissue and maternal plasma. In our previous study, we had shown that plasma omentin-1 level is decreased in women with GDM and increased after delivery. The aim of this study was to assess the maternal plasma omentin-1 level in the first trimester and its predictive value on development of GDM.
Materials and methods
Pregnant women in their first trimester ($n=220$) were included into the study. Those that developed GDM ($n=66$) was compared with non-diabetic pregnant women ($n=154$). WHO criteria was used for the diagnosis of GDM and screening was done at gestational weeks 24–28. Plasma omentin level was measured with ELISA. Fasting blood glucose and insulin were also measured and HOMA-IR was calculated.
Results
Patients with GDM was overweight compared to controls at the beginning of pregnancy (BMI: 28.2 ± 4.4 vs 25.2 ± 3.0). HOMA-IR was higher in GDM group (2.07 ± 1.4 vs 1.40 ± 0.6). Omentin level was not different between groups (2.22 ± 0.8 ng/l vs 2.05 ± 0.9 ng/l). After delivery plasma omentin level increased with a mean level of 166.6 ± 74.1 ng/l. There was no correlation between plasma omentin-1 level and glucose levels during oral glucose tolerance test. Omentin-1 level did not also correlate with BMI, HOMA-IR, and age.
Conclusion
Plasma omentin-1 level during early periods of pregnancy is did not differ between healthy and GDM-developed women. Since decreased levels were observed in GDM patients in previous studies, our findings could indicate that omentin-1 levels decrease as the pregnancy ages or change is only observed when GDM develops.

DOI: 10.1530/endoabs.37.EP356

EP357

The role of *TCF7L2* polymorphism in the development of type 2 diabetes in subjects with metabolic syndrome

Konstantinos Katsoulis[1], Stavroula Paschou[1], Elissavet Hatzi[2], Stelios Tigas[1], Ioannis Georgiou[2] & Agathocles Tsatsoulis[1]
[1]Department of Endocrinology, University of Ioannina, Ioannina, Greece; [2]Laboratory of Human Reproductive Genetics, University of Ioannina, Ioannina, Greece.

Introduction
Transcription factor 7 like-2 (*TCF7L2*) gene variants (rs12255372 and rs7903146) have been consistently shown to raise genetic risk for type 2 diabetes (T2D). The aim of this study was to investigate the possible role of these variants in the development of dysglycemia (T2D or impaired fasting glucose (IFG)) in patients with metabolic syndrome (MS).
Patients and methods
The study population consisted of 228 patients with MS who were divided in two groups. The first group consisted of 148 patients with MS and dysglycaemia (39M/109F, 59.8 ± 14.6 years) and the second group of 80 patients with MS without dysglycaemia (16M/64F, 56.1 ± 15.8 years). The diagnosis of MS was based on the criteria proposed by the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) Scientific Statement. The BMI and the waist circumference were recorded and blood samples were obtained after overnight fasting for biochemical tests. The rs12255372 and rs7903146 *TCF7L2* polymorphisms were genotyped in peripheral blood leucocytes.
Results
Genotype analysis revealed that the frequency of the T allele of the *TCF7L2* rs12255372 variant was 38.2% in the study population, while the frequency of the T allele of rs7903146 variant was 35.3%. The T allele of rs12255372 was more frequently present in patients with MS and dysglycaemia (48.3%) compared to patients with MS without dysglycaemia (19.4%) (OR: 3.89, 95% CI: 2.47–6.12, $P<0.0001$). Also, the T allele of the rs7903146 variant was more frequently found in patients with MS and dysglycemia (44.6%) compared to patients with MS without dysglycaemia (18.1%) (OR: 3.64, 95% CI: 2.29–5.78, $P<0.0001$).
Conclusion
The presence of variants rs12255372 and rs7903146 of the *TCF7L2* gene is associated with dysglycaemia (IFG and/or T2D) in patients with MS.

DOI: 10.1530/endoabs.37.EP357

EP358

Serum irisin level increases throughout the gestational period and it does not play role in development of gestational diabetes mellitus

Seda Seda[1], Hasan Aydın[2], Mehmet Sargın[3], Asuman Orçun[4], Ali Özdemir[5], Ayhan Çelik[6] & Gülgün Aslan[7]
[1]Division of Endocrinology and Metabolism, Fatih Sultan Mehmet Training and Educational Hospital, Istanbul, Turkey; [2]Division of Endocrinology and Metabolism, Yeditepe University Hospital, Istanbul, Turkey; [3]Diabetes Department, Kartal Lutfi Kirdar Training and Educational Hospital, Istanbul, Turkey; [4]Division of Biochemistry, Kartal Lutfi Kirdar Training and Educational Hospital, Istanbul, Turkey; [5]Department of Internal Medicine, Fatih Sultan Mehmet Training and Educational Hospital, Istanbul, Turkey; [6]Division of Obstetrics and Gynecology, Fatih Sultan Mehmet Training and Educational Hospital, Istanbul, Turkey; [7]Department of Internal Medicine, Kartal Lutfi Kirdar Training and Educational Hospital, Istanbul, Turkey.

Objective
Irisin is a novel adipomyokine that regulates the differentiation and phenotype of adipose tissue. It induces an increase in total body energy expenditure, improves insulin sensitivity, and glucose tolerance. It showed that the levels of irisin are low in obese, diabetic and impaired glucose tolerance patients. However, the information of the levels of circulating irisin in gestational diabetes mellitus (GDM) is controversial. In this study, we investigated i) the levels of irisin over the first and third trimester of gestation and ii) the change of irisin between first and third trimesters in GDM subjects.
Material and methods
Serum irisin was measured by an ELISA in a longitudinal prospective cohort study in 220 women. There are 154 healthy pregnant and 66 GDM women.
Results
The levels of irisin were low in the first trimester, but higher in the third trimester (0.76 ± 0.54 vs 1.32 ± 0.76, $P<0.0001$). There was a significant negative correlation between age (P: 0.002, r: −0.207), BMI (P: 0.03, r: −0.188) and weight in the first trimester (P: 0.03, r: −0.185) and HbA1c in the first trimester (P: 0.0001, r: −0.374). There was not any correlation between any parameters and the levels of irisin in the third trimester. The levels of irisin in the first trimester are low but high in the third trimester in the patients with GDM (0.62 ± 0.35 vs 1.26 ± 0.86, $P<0.0001$). But the levels were not different between women with GDM and healthy controls.
Conclusions
The levels of irisin are low in the first trimester but high in the later stage in third trimester. There is no effect of irisin on the development of GDM. The physiological significance of these findings needs to be assessed in future experiments.

DOI: 10.1530/endoabs.37.EP358

EP359

Gestational diabetes mellitus may associate with atherosclerosis due to high mean platelet volume which is a determined of platelet function

Senay Arikan Durmaz[1], Ayse Carlioglu[2], Bilge Eris[1], Faruk Yildiz[2] & Halime Kiliç[3]
[1]Department of Endocrinology and Metabolism, Kirikkale University, Kirikkale, Turkey; [2]Department of Endocrinology and Metabolism, Erzurum Region Education and Research Hospital, Erzurum, Turkey; [3]Department of Gynecology and Obstetrics, Nenehatun Doğumevi Hospital, Erzurum, Turkey.

Aim
Mean platelet volume (MPV), which is a determinant of platelet function, is an independent risk factor for atherosclerosis. The aim of this study is to evaluate MPV values in gestational diabetes mellitus (GDM).
Material and methods
Forty-nine women with gestational diabetes mellitus (mean age 28.2 ± 4.7 years) and 40 healthy pregnant women (mean 26.2 ± 4.6 years age) who came to our Out-Patient Clinic of Endocrinology were included in the study. GDM group and the control group were matched for age. All the study subjects were evaluated by platelet parameters. All complete blood count analysis was performed with an automatic hematologic analyser.
Result
The MPV levels in GDM were significantly higher than those control group (7.9 ± 0.6 and 7.6 ± 0.54 fl, respectively; $P = 0.0001$). In addition, there was found a positive correlation between MPV and fasting glucose (FG) levels ($r = 0.52$; $P = 0.03$). The multiple regression analysis of MPV was performed. High MPV value in GDM was independent from age, BMI, and FG levels ($\beta = 0.238$, $P = 0.046$). No statistically significant differences were found for the other parameters such as haemoglobin, platelet count, lymphocyte count, neutrophil count, white blood cell count, platelet distribution width, and plateletcrit.
Conclusion
Our findings suggest that GDM are susceptible to increased MPV values, which contribute to increased risk of atherosclerosis. Future prospective studies that MPV was compared with other risk factors of atherosclerosis are required to determine their clinically importance in GDM.

DOI: 10.1530/endoabs.37.EP359

EP360

Role of nitrosative and oxidative stress on the development of gestational diabetes mellitus and their effect in GDM placenta

Cristina López-Tinoco, Francisco Visiedo, Celeste Rosendo, María Belén Ojeda, Isabel Mateos, Carmen Segundo & Manuel Aguilar-Diosdado
Hospital Puerta del Mar, Cádiz, Spain.

Background and aims
The relationship between gestational diabetes mellitus (GDM) and oxidative stress is not well known and the effect of both oxidative and nitrosative stress in GDM placenta and the impact that could have on perinatal morbidity and risk of future complications is still pending to be elucidated. The aim of the study was to evaluate the relationships between maternal and placental tissue levels of markers of nitrosative and oxidative stress and antioxidants in women with GDM, which potentially may have considerable clinical implications in the pathogenesis and/or the evolution of GDM.
Material and methods
Pregnant women ($n = 78$; 53 with GDM, 25 controls), between the 24th and 29th weeks of gestation were enrolled. Both groups were analysed for demographic data, perinatal and obstetrics results and the levels of the markers oxidative stress and antioxidants status were measured (measured in serum or plasma using a commercial kit (Cayman Chemical, Ann Arbor, MI, USA)). Seven placenta GDMs and seven normal placentas were studied. Placental tissue levels of markers of oxidative stress and antioxidant were measured by Western Blotting techniques and Biotin-switch technique has been performed to identify *S*-nitrosylated protein in placental tissue.
Results
In the univariate analysis control versus patient results were: pre-gestational BMI 23.31 ± 4.2 kg/m^2 vs 27.13 ± 4.6 kg/m^2 ($P = 0.001$); weeks at delivery 39.2 ± 3.05 vs 38.9 ± 1.8 ($P = 0.09$); caesarean delivery 12.5% vs 43% ($P = 0.004$); macrosomia 4% vs 9.4% ($P = 0.6$); lipoperoxides (LPO) 2.06 ± 1.00 mol/mg vs 3.14 ± 1.55 mol/mg ($P = 0.001$); catalase 3.23 ± 1.41 nmol/min per ml vs 2.52 ± 1.3 nmol/min per ml ($P = 0.03$); superoxide dismutase (SOD) 0.11 ± 0.04 U/ml vs 0.08 ± 0.01 U/ml ($P = 0.0003$); glutathione peroxidase (GPX) 0.03 ± 0.006 nmol/min per ml vs 0.025 ± 0.006 nmol/min per ml ($P = 0.01$); glutathione reductase (GSH) 0.004 ± 0.002 nmol/min per ml vs 0.004 ± 0.004 nmol/min per ml ($P = 0.9$); and glutathione transferase (GST) 0.0025 ± 0.0012 nmol/min per ml vs 0.0027 ± 0.00017 nmol/min per ml ($P = 0.7$). Multivariate analysis that was performed using non-conditional logistic regression showed catalase might have a protective effect and LPO seems to be a risk factor for GDM development. In GDM placenta, protein expression of catalase ($n = 0.05$), SOD ($n = 0.03$), and GPx ($n = 0.04$) were significantly increased. In addition, an increased *S*-nitrosylation of catalase ($n = 0.02$), SOD, and GPx has been determinate in GDM placenta comparing with control.
Conclusions
i) An increase in oxidative stress and a decrease in antioxidative defence can be observed in plasma of women with GDM. However, in placental tissue, elevated expression of antioxidant enzymes and an increment of their *S*-nitrosylation have been found which could be related with regulation of these activity. ii) Results suggest that resistance to oxidative insults generated in placenta by a chronic mild oxidative/nitrosative environment could alleviate the effect of systemic elevation of ROS and RNS. The effect of both oxidative and nitrosative stress in GDM placenta and the impact that could have on perinatal morbidity should be studied more extensively.

DOI: 10.1530/endoabs.37.EP360

EP361

Dynamic thiol/disulfide homeostasis in patients with newly diagnosed type 2 diabetes mellitus

Nergiz Bayrakci[1], Ihsan Ates[2], Nihal Ozkayar[1], Fatma Meric Yilmaz[3,4], Canan Topcuoglu[3], Salim Neselioglu[4], Ozcan Erel[4] & Mustafa Altay[1]
[1]Department of Nephrology, Ankara Numune Education and Research Hospital, Ankara, Turkey; [2]Department of Internal Medicine, Ankara Numune Education and Research Hospital, Ankara, Turkey; [3]Department of Biochemistry, Ankara Numune Education and Research Hospital, Ankara, Turkey; [4]Department of Biochemistry, Faculty of Medicine, Yildirim Beyazit University, Ankara, Turkey.

Background
Thiol/disulfide homeostasis plays an important role in antioxidative defense mechanism, detoxification, signal transport, management of enzyme activity and trascription factors, and apoptosis. When thiol/disulphide homeostasis breaks down, these important cellular functions get deranged. Pathologies secondary to oxidative stress are seen in organeles in which this homeostasis is deranged. The aim of the study was to investigate dynamic thiol/disulfide homeostasis in newly diagnosed type 2 diabetes mellitus.
Materials and methods
Blood thiol/disulfide homeostasis status, that consists of native thiol–disulphide exchanges, was investigated in 60 patients (22 males and 38 females) diagnosed with type 2 diabetes mellitus and 60 healthy control subjects (25 males and 35 females). Serum native thiol and total thiol concentrations were measured as a paired test. The half of the difference between total thiol and native thiol concentrations gave the disulphide bond amount.
Results
In comparison to the control group, patients with diabetes mellitus had lower levels of serum thiol and total thiol (340.7 ± 46.1 μmol/l vs 313.7 ± 57.4 μmol/l; $P = 0.005$ and 366.7 ± 46.7 μmol/l vs 343.7 ± 59.0 μmol/l; $P = 0.020$ respectively) while higher average disulfide level (12.9 ± 3.2 μmol/l vs 15.0 ± 4.6 μmol/l; $P = 0.008$). In patients with diabetes mellitus, average disulfide/thiol ratio (%) (3.9 ± 1.2 vs 5.0 ± 1.6; $P = 0.001$) and disulfide/total thiol ratio (%) (3.6 ± 1.0 vs 4.5 ± 1.6; $P = 0.001$) was higher while average thiol/total thiol ratio (%) was lower (92.8 ± 2.1 vs 91.0 ± 3.4; $P = 0.001$) than the control group. HbA1c level and age correlated positively with serum disulfide/thiol ratio and disulfide/total thiol ratio ($r = 0.239$, $P = 0.009$ and $r = 0.228$, $P = 0.012$ respectively) while thiol/total thiol ratio was correlated negatively ($r = -0.228$, $P = 0.012$).
Conclusion
A tendency towards disulfide formation in thiol/disulfide homeostasis was found in patients with diabetes mellitus and there was a positive correlation between HbA1c and disulfide/thiol ratio.

DOI: 10.1530/endoabs.37.EP361

EP362

The growth patterns in children born to mothers with gestational diabetes mellitus

Joanna Rutkowska, Elzbieta Bandurska-Stankiewicz, Dorota Wiatr-Bykowska, Katarzyna Myszka-Podgórska, Ewa Kuglarz & Wojciech Matuszewski
Endocrinology, Diabetology and Internal Medicine Clinic, University of Varmia and Masuria, Olsztyn, Poland.

Introduction
The aim of the study was to assess if gestational diabetes mellitus (GDM) influence the pregnancy outcomes and the growth patterns in children.
Design
Our prospective study cohort consisted of 261 children born to mothers with GDM and 153 control children born to non-diabetic mothers. In both groups children's weight, length were assessed. Children were matched for large for gestational age (LGA) (birth weight >90th percentile for gestational age), appropriate for gestational age (AGA) (birth weight between the 10th and 90th percentiles), and small for gestational age (SGA) (birth weight <10th percentile) status. Children anthropometric measurements were made at 12, 18, 24, and 30 months. BMI was calculated. The overweight was diagnosed at BMI between 90 and 96 percentiles, obesity between 97 and 100 percentiles. The WHO child growth standards were implemented. The bioethics committee agreement was obtained.
Results
Among 261 GDM children, 80.5% were AGA, 10% SGA, 9.6% LGA; in control group 19% LGA. Birth weight of the child in GDM pregnancies was 3.30 ± 0.53 kg comparing to the control children 3.42 ± 0.54 kg, $P=0.01$. No changes in weight and BMI were found between groups in the 12th month of life. The weight >90 percentile at this period was observed in 34.6% children, BMI between 90 and 96 percentiles in 17.33% and between 97 and 100 percentiles in 17.33%. At the age of 18 months the weight of childrem born to GDM mothers was >90 percentle in 54.8% comparing to the control group in 29%, $P=0.04$; No changes were found in BMI. At the age of 24 and 30 months we found no differences in BMI in both groups.
Conclusions
We found that children who were LGA at birth were less often born to GDM mothers after implementation of dietary regiment comparing to general population. GDM did not influence the growth pattern in first 36 months of live.
Disclosure
Supported by: Polish Ministry of Science Grant Number NN404 521938.

DOI: 10.1530/endoabs.37.EP362

EP363

Insulin resistance is associated with larger thyroid volume in adults with type 1 diabetes

Anita Rogowicz-Frontczak, Stanislaw Pilacinski, Anna Chwialkowska, Bogna Wierusz-Wysocka & Dorota Zozulinska-Ziolkiewicz
Department of Internal Medicine and Diabetology, University of Medical Science, Poznan, Poland.

Background
Larger thyroid volume and nodular thyroid disease were found to be associated with insulin resistance (IR) in patients with type 2 diabetes (T2DM). Similar analyses is lacking in T1DM.
Aims
To check the association between thyroid volume and IR using estimated glucose disposal rate (eGDR) in patients T1DM.
Materials and methods
We included 99 consecutive patients with T1DM aged 29 (mean, S.D.=6) with diabetes duration 13 (6) years. Exclusion criteria were: history of thyroid disease, current treatment of L-thyroxine or anti-thyroid drugs. Anti-thyroid peroxidase (ATPO), anti-thyroglobulin (ATg) antibodies, and anti-TSH receptor antibodies (TRAb) were determined. Assays for TSH and free thyroid hormones (trijodothyronine, fT_3, and thyroxine (fT_4)) were also performed. Thyroid was measured using ultrasonography. IR was assessed using eGDR, calculated according to the formula $(24.4 - 12.97 \times \text{WHR} - 3.39 \times \text{HT} - 0.60 \times \text{HbA1c})$, where WHR -waist-to-hip ratio and HT – history of hypertension (yes=1 and no=0).
Results
The prevalence of thyroid autoimmunity (positivity for ATPO, ATg, or TRAb) in the study group was 31%. Subclinical hypothyroidism was diagnosed in 7%, and overt hypothyroidism in 2% of patients. Mean (S.D.) thyroid volume was 15.6 (6.2) ml in patients with eGDR ≤ 7.5 (patients with IR) and 11.7 (4.7) ml in patients with eGDR above 7.5 ($P=0.002$). Thyroid volume correlated inversely with eGDR ($r=-0.35$, $P<0.001$). In multivariate linear regression model association between thyroid volume and eGDR was independent from sex, duration of diabetes, BMI, TSH, and presence of thyroid autoimmunity (β: -0.22, $P=0.025$).
Conclusion
Lower insulin sensitivity is associated with larger thyroid volume in patients with T1DM independently from BMI and signs of autoimmune thyroid disease.

DOI: 10.1530/endoabs.37.EP363

EP364

Rate of impaired glucose regulation in outpatient care

Lina Zabuliene[1,2], Birute Pauliukiene[2] & Jurgita Urboniene[3]
[1]Clinics of Rheumatology, Traumatology – Orthopaedics and Reconstructive Surgery, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [2]Antakalnio Outpatient Clinic, Vilnius, Lithuania; [3]Infectious Diseases and Tuberculosis Hospital, Vilnius University Hospital 'Santariskiu klinikos', Vilnius, Lithuania.

The objective was to assess rate of impaired glucose regulation and progression to diabetes in adults using routinely collected health-care data.
Material and methods
We conducted an audit on results of 75-g standardized oral glucose tolerance tests (OGTT) performed at Vilnius Antakalnio Outpatient Clinic from 3rd Jan 2011 to 15th Dec 2014 and analysed data of adult patients. We excluded from analysis results of 358 patients who didn't perform 2-h plasma glucose concentration (2 h PG) test. 5575 patients' data were included into analysis. We applied 2006 World Health Organization criteria for diabetes, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG).
Results
Mean patients' age was 53.64 ± 15.59 years. 36.4% of the patients were men and 63.6% were women. Mean fasting plasma glucose (FPG) concentration was 5.87 ± 0.65 mmol/l, mean 2 h PG was 6.20 ± 2.25 mmol/l. FPG in women was lower than in men (5.79 ± 0.67 mmol/l vs 6.03 ± 0.60 mmol/l, $P<0.001$), but 2 h PG was higher in women than in men (6.25 ± 2.14 mmol/l vs 6.09 ± 2.44 mmol/l, $P=0.011$). Mean 2 h PG increased with age. OGTT detected diabetes in 286 (5.1%) patients. 778 (14.0%) patients met criteria for IGT and 1518 (27.2%) for IFG. Normal glucose tolerance was found in 2993 patients. The rate of impaired glucose regulation increased with age achieving peak in groups of 50–59 and 60–69 years old patients (27.3 and 23.4% respectively). 787 patients came back for repeated OGTT. Repeated OGTT revealed 48 new cases of diabetes. Before developing diabetes 58.3% patients had IGT, 22.9% had IFG, and 18.8% had normal glucose tolerance. Mean time from the first OGTT to diabetes development was 18.15 ± 9.36 months. Female gender (OR=2.42, $P=0.028$) and IGT (OR=6.08, $P<0.001$) predicted diabetes.
Conclusion
This analysis revealed that the rate of undiagnosed diabetes is 5.1%; nearly half of outpatients with risk factors for diabetes have impaired glucose regulation. Women with IGT have higher risk for diabetes development.

DOI: 10.1530/endoabs.37.EP364

EP365

The prevalence of diabetes and associated risk factors among adult population in a Turkish population (Trabzon city)

İrfan Nuhoğlu, Cihangir Erem, Halil Önder Ersöz, Mustafa Koçak & Nadim Civan
KTÜ TIP FAK, Trabzon, Turkey.

Objective
The objectives of this study were to determine the prevalence of diagnosed and undiagnosed diabetes mellitus (DM), prediabetes and to evaluate the associated risk factors in the sample of adult Turkish population.
Methods
A total of 4000 eligible study subjects aged 20 years or older, chosen by multistage sampling on a field were selected. Of those 3721 subjects (2139 women and 1582 men) participated in the study. The study was performed between January 2010 and September 2012 in central Trabzon and its ten town.
Results
The prevalences of prediabetes and DM were found to be as 6.4 and 10.4% (newdiagnosed 3.6%) respectively. There was no a significant difference between men and women for the prevalence of diabetes. Diabetic prevalence was found to

increase significantly by aging in both genders ($P<0.0005$). The prevalence reached its peak level in age group of ≥ 70 years (29.2%). In multivariate logistic regression analysis, advanced age (OR: 21.6 in the 60–69 age group and OR: 26.7 in the group 70 years and over), marriage (OR: 2.05), housewives (OR: 1.34), high monthly income (OR: 2.52 in the group of income ≥ 2250 TL), positive family history of diabetes (OR: 2.84), overweight (OR: 1.61), obesity (OR: 2.25), hypertension (OR: 1.42), and dyslipidaemia (OR: 1.38) were independent risk factors for the development of diabetes.

Conclusion

DM is an important health problem in the adult population of Trabzon city. It seems that the prevalence of diabetes is increasing in our region as well as our country and the world. New diagnosed diabetic patients who are unaware of their status are at high risk. To control DM and associated risk factors, effective public health education and taking urgent steps including serious education and teaching, providing a well-balanced diet and increasing physical activity are needed.

DOI: 10.1530/endoabs.37.EP365

EP366

Diabetes mellitus in patients with rheumatoid arthritis

Ifigenia Kostoglou-Athanassiou[1], Aikaterini Tzanavari[2], Theodota Banti[2], Charoula Katsavouni[2], Natalia Kalaycheva[2] & Panagiotis Athanassiou[2]
[1]Department of Endocrinology, Red Cross Hospital, Athens, Greece;
[2]Department of Rheumatology, St. Paul's Hospital, Thessaloniki, Greece.

Introduction

In rheumatoid arthritis (RA) glucose metabolism may be affected either by the autoimmune inflammatory disease itself, or by the treatment used to manage the disease. Metabolic syndrome seems to be prevalent in RA patients.

Aim

The aim was to study the prevalence of diabetes mellitus type 2 and metabolic factors related to the development of atherosclerosis within a cohort of RA patients cared for within a single Rheumatology Department.

Methods

Within a cohort of 204 RA patients, aged 29–88 (mean $\pm$ S.E.M.) 62.87 $\pm$ 08.86 years the incidence of diabetes mellitus and metabolic factors related to the development of atherosclerosis was studied. In the cohort of RA patients ESR was 37.12 $\pm$ 1.57 mm/h, CRP 1.56 $\pm$ 0.15 mg/dl, and the disease activity index DAS28 was 3.80 $\pm$ 0.13, 49% being positive for rheumatoid factor and 23% having positive anti-CCP antibodies.

Results

Within the cohort of 204 RA patients 45 (22.06%) were found to suffer from diabetes mellitus type 2, five being on therapy with a combination of insulin and oral antidiabetic agents, ten on oral antidiabetic agents, and the rest on diet only. Within the cohort of RA patients morning glucose concentration was 110 $\pm$ 2.6 mg/dl (mean $\pm$ S.E.M.), cholesterol concentration 200.3 $\pm$ 2.98 mg/dl, HDL cholesterol 55.64 $\pm$ 1.18 mg/dl, LDL cholesterol 123.19 $\pm$ 2.41 mg/dl, and triglyceride 125.4 $\pm$ 3.7 mg/dl. Within the cohort of RA patients 33 had hyperlipidemia requiring therapy with lipid lowering agents, mainly statins and in two cases a combination of statin and fenofibrate.

Conclusions

Diabetes mellitus type 2 seems to be prevalent amongst patients with RA, hyperlipidemia being also prevalent. The disease itself, which is related to an autoimmune inflammatory process and the medications required for its management may affect blood glucose metabolism adversely.

DOI: 10.1530/endoabs.37.EP366

EP367

Correlation between fasting plasma glucose levels and HbA1c for diagnosis of prediabetes and diabetes: the 2011 Korea National Health and Nutrition Examination Survey

Sung-Hee Ihm, Jun Goo Kang, Chul Sik Kim, Seong Jin Lee, Yoon Jung Kim, Ju Ri Park, Sung Hoon Yu, Ohk Hyun Ryu, Eun Gyung Hong, Doo-Man Kim, Jae Myung Yoo, Moon Gi Choi, Ho Young Son & Hyung Joon Yoo
Hallym University Sacred Heart Hospital, Anyang, Republic of Korea.

Aim

HbA1c is recommended as a diagnostic criterion for diabetes in clinical practice guidelines for type 2 diabetes in 2011 (10). Although there have been several reports that compared HbA1c-based diagnosis for diabetes with glucose-based diagnosis in Koreans, it is thought that larger epidemiological studies are required to confirm the association of HbA1c and FPG for diagnosis of diabetes for the Korean population. We conducted this study to examine the relationship between FPG and HbA1c levels measured for diagnosis of diabetes and assess the differences in FPG and HbA1c values according to the HbA1c-based and FPG-based diagnosis of diabetes recommended from the ADA in the recent Korea National Health and Nutrition Examination Survey (KNHANES).

Methods

KNHANES, conducted periodically by the Korea Centers for Disease Control and Prevention and initiated in 1998, designed to provide comprehensive information of Korean on health status, health behavior, and nutritional status. Data from second (2011) years KNHANES V (fifth) which samplings include HbA1c over 10 years old men and women and fasting blood glucose were used in this cross-sectional analysis. From an initial total of 8518 men and women, 6066 persons (2677 men and 3389 women), with HbA1c and fasting glucose data and without diabetic medications, were evaluated. From 6066 persons, 1585 were excluded for several reasons. Baseline characteristics are presented as means for continuous variables, and proportions for categorical variables. The association of fasting blood glucose and HbA1c was examined using linear regression models.

Results

We found the results of linear regression analysis in the study population and in the subjects with diabetes by FBS criteria only. FPG 100 mg/dl, predicted HbA1c 5.75% in the study population and 5.76 in the subjects with diabetes by FBS criteria only respectively. FPG 126 mg/dl also predicted HbA1c 6.4 and 6.44%. However, in the subjects with diabetes by HbA1c criteria only, FPG 100 mg/dl, predicted HbA1c 6.49%, FPG 126 and 130 mg/dl, and predicted HbA1c 7.14 and 7.24% respectively.

Conclusions

This study is the first epidemiological report showing that an association between HbA1c and FPG levels for the diagnosis of prediabetes and diabetes is consistent with ADA recommendations in over 19 years old Korean population without diabetic medications. This conclusion requires further study to compare the characteristics of individuals with newly diagnosed diabetes by each only HbA1c- and only FPG-based diagnostic criteria and large-scale longitudinal study to assess the relation of HbA1c to incident diabetic retinopathy.

DOI: 10.1530/endoabs.37.EP367

EP368

Blood lead is associated with impaired fasting glucose in middle-aged population: the 2008–2011 Korean National Health and Nutrition Examination Survey

Sang Yong Kim & Jin Hwa Kim
Chosun University Hospital, Gwang-Ju, Republic of Korea.

Objective

Environmental exposure to heavy metals has affected human health. Several studies have suggested that lead increase oxidative stress and induce mitochondrial dysfunction. The objective was to determine whether there was an association between blood lead level and impaired fasting glucose (IFG) in middle-aged population.

Research design and methods

This study was based on the data from the Korean National Health and Nutrition Examination Survey (KNHANES), conducted by the Korean Ministry of Health and Welfare in 2008–2011. Of 37 753 participants, data for 2366 adults ≥ 40 years of age without diabetes were included in the analysis. Subjects were subdivided according to quartile of blood lead level. Multivariate logistic regression analyses were used to identify whether there was an independent association between blood lead level and IFG by adjusting for confounding factors.

Results

Blood concentration of lead was significantly higher in IFG group, compared with normal glucose tolerance (NGT) group (IFG, 2.723 $\pm$ 0.565 μg/dl and NGT, 2.522 $\pm$ 0.384, $P=0.002$). The prevalence of IFG increased significantly by increasing quartile of blood lead level (Q1, 20.6%; Q2, 21.6%; Q3, 26.7%; and Q4, 31.1%; $P=0.001$). After fully adjusting for confounding factors, including lifestyle behaviors, sociodemographic factors, family history of diabetes, and known diabetes risk factors, the fourth quartile of blood lead level (>3.091 μg/dl) was significantly associated with IFG (odds ratio 1.491 (95% CI 1.004–2.214)).

Conclusions

Blood lead level was independently associated with IFG in middle-aged population. We propose that the lead may contribute to increasing glucose level and risk of prediabetes.

DOI: 10.1530/endoabs.37.EP368

EP369

The state of superoxidedismutase activity as marker of oxidative stress in patients with impaired glycaemic states

Volha Shyshko[1], Tatjana Mokhort[1], Natalia Tsapaeva[1], Inna Buko[2] & Elena Konstantinova[3]
[1]Belarussian State Medical University, Minsk, Belarus; [2]Belarussian Republic Center of Cardiology, Minsk, Belarus; [3]A.V.Luikov Heat and Mass Transfer Institute of the National Academy of Science, Minsk, Belarus.

One of the key enzymes of antioxidant system is superoxide dismutase (SOD) that catalyses dismutation of superoxide anionic radical ($O_2^{\cdot -}$)l to molecular oxygen (O_2) and hydrogen (H_2O_2). It was revealed that activity of SOD is decreased in patients with decompensated type 2 diabetes (T2D) but there is insufficient data about enzyme activity in compensated states and prediabetes.

Purpose

To analyse the state of SOD activity in patients with compensated T2D and prediabetes.

Materials and methods

195 patients were divided into five groups: group 1 – 23 patients with impaired fasting glucose (IFG), group 2 – 23 patients with impaired glucose tolerance (IGT), group 3 – 41 patients with T2D, group 4 – 48 patients with T2D and concomitant coronary heart disease (CHD), and group 5 – 41 almost healthy person (control). All patients were before 60 years old and patients with T2D had compensated glycaemic state. Activity of SOD was measured by reduction of nitrotetrazolium by superoxide radical.

Results

The lowest activity was registered in group 4 (71.71 (48.14; 80.37) CU/ml) and in group 3 (76.49 (35.43; 85.22) CU/ml) compared to control group (104.96 (66.86; 142.82) CU/ml) ($P4–5 < 0.001$ and $P3–5 < 0.005$). Activity of SOD was significantly higher in patients with IGT (92.95 (60.21; 144.02)) compared to other groups ($P2–3 < 0.005$ and $P2–4 < 0.001$) and almost was not different compared to almost healthy person ($P > 0.1$). We didn't reveal any significance in activity of SOD on patients with IFG and other groups.

Conclusion

T2D is associated with decreased activity of SOD which is more significant when associated with CHD. Prediabetes is not associated with changes in the activity of SOD.

DOI: 10.1530/endoabs.37.EP369

EP370

Comparison between aldosterone and renin measurement by chemiluminescent immunoassay and RIA for the diagnosis of primary aldosteronism

Jacopo Burrello[1], Fabrizio Buffolo[1], Silvia Monticone[1], Tracy Ann Williams[1], Andrea Viola[1], Giulio Mengozzi[2], Franco Veglio[1] & Paolo Mulatero[1]
[1]University of Torino, Torino, Italy; [2]Città della Salute e della Scienza, Torino, Italy.

Objective

Primary aldosteronism (PA) is the most frequent cause of secondary hypertension. According to the Endocrine Society Guidelines, up to 50% of hypertensive patients should be screened for PA, using the aldosterone to renin (or plasma renin activity (PRA)) ratio (AARR and ARR respectively). The automated Diasorin LIAISON chemiluminescent immunoassay for renin and aldosterone measurement became available and in many laboratories is currently used instead of the classical radioimmunometric PRA and aldosterone assay. Aim of the study was to prospectively compare the diagnostic accuracy of AARR and ARR as screening test for PA and the two aldosterone assays also during confirmatory test in patients with a positive screening test.

Design and methods

100 patients were screened for PA and 44 patients underwent confirmatory test (i.v. saline load or captopril challenge test). We considered as cut off for the AARR 2.7 (ng/dl/mU/l) and for the ARR 30 (ng/dl/ng/ml/h). All patients positive to one of the two screening test underwent confirmatory test; patients with positive confirmatory test underwent subtype diagnosis by CT scanning and adrenal vein sampling.

Results

73 patients were diagnosed as essential hypertensives, 22 had bilateral adrenal hyperplasia, and five had an aldosterone producing adenomas (APA). The AARR displayed a sensitivity of 78% and a specificity of 100%, whereas the ARR had a sensitivity of 96% and a specificity of 90%. Of the 6/27 PA patients missed by AARR, none resulted to be affected by APA. All PA patients were correctly diagnosed by chemiluminescence at confirmatory test. In the overall sample of 181 measurements available both the correlation for the PRA with renin and for aldosterone in chemiluminescence and RIA were highly significant ($\rho = 0.66$, $P < 0.0001$ and $\rho = 0.80$, $P < 0.0001$ respectively). On ROC curves, the AUC for AARR was 0.905 (95% CI 0.821–0.988) and for ARR 0.947 (95% CI 0.903–0.991) were not significantly different.

Conclusions

The automated aldosterone and renin chemiluminescent assay is a reliable alternative to the well-established radioimmunometric method, especially for the detection of APA.

DOI: 10.1530/endoabs.37.EP370

EP371

Listening to the patient's story: a qualitative approach to pre-gestational diabetic pregnancy

Catherine O'Hare[1] & Richard Greene[1,2]
[1]University College Cork, Cork, Ireland; [2]Cork University Maternity Hospital, Cork, Ireland.

Pre-gestational diabetics frequently rise to the challenge of pregnancy with remarkable improvements in diabetic control. Optimising pregnancy outcomes necessitates rigorous diabetes self-care, which is critically dependent on women's capacity and the support they receive. The aim of this study was to identify self-reported drivers and inhibitors of self-care in pre-gestational diabetic pregnancies. The study was carried out at a tertiary referral maternity unit. Convenience sampling was used. Ten women were recruited: age range 20–40 years, median age 33 years; nine type 1 diabetics; one type 2 diabetic; duration of diabetes ranged from 1 to 33 years, median was 16.5 years; 6 were unplanned pregnancies; six primigravida; two received diagnosis of foetal complications. Baseline Hba1c ranged from 42 to 85 mmol/l, median was 73 mmol/l. Follow-up measures ranged from 35 to 53 mmol/l, median was 48 mmol/l. Qualitative methods were employed to extract novel insights. We interviewed ten pregnant diabetics using six open-ended questions. Audio recordings were transcribed and 'computer assisted qualitative data analysis software' (CAQDAS) assisted coding and analysis of transcripts. Content analysis of transcripts revealed numerous themes. In addition, changes in self-care during pregnancy were measured using a validated questionnaire, 'Summary of Diabetes Self-Care Activities' (SDSCA). Nine women reported being highly motivated, driven predominantly by concern for baby's wellbeing. Numerous challenges were identified: difficulty maintaining a strict diet, hypoglycaemia, turbulent blood glucose and emotional challenges. Women perceived the glycaemic targets as demanding. In contrast numerous supports were perceived to facilitate self-care, particularly the diabetic care team. Other supports were family and the working environment. Regular daily routine was viewed as crucial. The 'SDSCA' questionnaire surprisingly did not detect significant changes, yet considerable changes in self-care were reported at interview. In conclusion, pre-gestational diabetic women are highly self-motivated as shown by this qualitative research. 'SDSCA' was not sensitive in this setting.

DOI: 10.1530/endoabs.37.EP371

EP372

Biorhythms of contrinsular hormones in pregnant with type 1 diabetes receiving insulin with pump therapy and multiple injections

Tatsiana Mokhort[1], Tatsiana Skryplionak[2], Olga Pancratova[2] & Vladislav Rimashevskiy[3]
[1]Belarusian State Medical University, Minsk, Belarus; [2]«Mother and Child» National Research Center, Minsk, Belarus; [3]Belarusian Medical Academy of Post-graduated Education, Minsk, Belarus.

Pregnancy affects on the course type 1 diabetes (T1D), which is a result of changes in the production of hormones and their biorhythms.

Aim

To examine circadian biorhythms of contrinsular hormones (BCh) contribution in the morning postprandial glycaemia depending on the type insulin therapy.

Materials and methods

The study involved of 91 pregnant with T1D in 31–34 weeks on a background the maximum insulin resistance. Evaluation of circadian BCh (cortisol, progesterone, and placental lactogen) held on the results of the ELISA (DRG, Germany) serum samples, picks up in 0300, 0700, 1200, 1700, and 2200 h.

Results
The estimation of cortisol levels dynamics in acrophase marked invariable, which accounted at 0700 h, and minifase at 0300 h regardless of the type of insulin therapy. The acrophase of placental lactogen accounted at 1700 h, at the same time minifase at 2200 h and does not depend on the type of insulin therapy. The opposite results we get after estimation of progesterone levels. Progesteron acrophase accounted at 1700 h on the pump therapy and at 2200 h on multiple injections of insulin. Minifase of progesterone in both cases accounted at 0700 h.
Conclusion
Expressed of insulin resistance in the first half of the day determine the need for the use of high carb ratios for breakfast in order to achieve target levels of postprandial glycaemia is caused by cortisol acrophase and not placental lactogen and progesterone, which are laminated to the maximum mezor these hormones in third trimester. The use of pump insulin therapy accompanied by a shift of progesterone acrophase.

DOI: 10.1530/endoabs.37.EP372

EP373

Higher glucose levels and prevalence of prediabetes in patients with autoimmune thyroiditis

Georgios Boutzios, Krystallenia Alexandraki, Stavros Liatis, Eleni Lampropoulou, Georgios Nikolopoulos, Aikaterini Bouki, Eleni Papaoiconomou, Kokkona Paradeisi, Nikolaos Tentolouris & Gregory Kaltsas
Section of Endocrinology, Department of Pathophysiology, National and Kapodestrian University of Athens Medical School, Athens, Greece.

Introduction
Thyroid autoimmunity and diabetes mellitus type 2 (DM2) are the commonest endocrine disorders in the general population. The aim of the study was to investigate whether there is an association between thyroid autoimmunity and β-cell secretion in patients with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT).
Methods/design
501 patients (381 females) 46.5±14.2 years with IFG and/or IGT and autoimmune thyroiditis (AIT, TgAb, and/or TPOAb positive) were included in the study. Characteristics recorded were age, gender, waist circumference (cm), and BMI (kg/m^2). Fasting glucose (mg/dl) and insulin levels (μIU/ml), glucose 120 min post-oral glucose tolerance test (OGTT), HbA1c (%), HOMA and QUICKI insulin-resistance (IR) indices, and IR status as HOMA >2.16 and OUICKI <0.34 were also assessed. In 291 patients who had an oral glucose tolerance test (OGTT) with glucose and insulin measurement in five different time points), first, second phase insulin sensitivity index (ISI) and ISI were also assessed. Patients with hypothyroidism and DM2 were excluded from the study.
Results
Patients (n=266) who had AIT compared to non-AIT patients (n=) were older (48.6±13.5 vs 44.1±14.66 (P=0.001)), had larger waist (95.4±15.6 vs 91.4±15.5 (P=0.007)), higher glucose levels (99.9±12 vs 95.5±12.5 (P<0.001)), and higher prediabetes rates (64.2%) (χ^2=27.2, P<0.001) but similar rates of IR (51.8%). Prediabetic (P=64) patients with AIT had first phase ISI: 1293.8±774.6, second phase ISI: 432.3±231.8, and ISI: 0.06±0.05 comparable albeit higher to non-AIT (first phase ISI: 934.3±670.5 second phase ISI: 324.8±207.9, and ISI: 0.07±0.05) but similar ISI (P=0.06, P=0.06, and P=0.6 respectively).
Conclusion
Patients with AIT and impaired β-cell secretion had higher HbA1c levels with similar rate of insulin resistance and higher prevalence of prediabetes compared to non-AIT. Thyroid autoimmunity could be eventually a possible factor modifying β-cell secretion. Nevertheless further studies are needed to confirm these findings.

DOI: 10.1530/endoabs.37.EP373

EP374

Effectiveness of Aβ classification of diabetes prone to ketosis in real clinical practice

Natalia Volkova, Maria Porksheyan & Julia Rudakova
Rostov State Medical University, Rostov on Don, Russia.

Introduction
Prevalence of so-called diabetes prone to ketosis (DPK), has been increasing. The necessity of lifelong insulinotherapy is determined by Aβ classification of DPK.
Design
Seven patients with atypical course of T2DM were studied. All patients had gradual development of hyperglycemia, obesity 1–2 stages, and acetonuria. Noone had acute weight loss. Stage 3 had positive GAD-AB, stage 4 – negative. Initially all patients were treated by insulin during 2–3 weeks. Thereafter, C-peptide was determined and type of diabetes, prone to ketosis, was established. If C-peptide was more than 1.2 ng/ml, oral hypoglycemic drugs were prescribed. Patients were followed up during 1 year with studying BMI, C-peptide, HbA1c, and acetonuria.
Results
Three patients had diagnosis of A+β+DPK and took oral medicine. However, during 1-year follow up, all these patients had HbA1c greater 7.5%, unmotivated weight loss and periodical acetonuria. After 6-month of follow up C-peptide was <1.2 ng/ml at all patients, which was an indication to lifelong insulinotherapy. Four patients were diagnosed with DPK A−β+ and took oral medicine. During 1-year follow up, 2 patients had HbA1c <7.5% and no cases of acetonuria. With stable weight, the level of C-peptide was still >1.2 ng/ml at the end of follow up. Thus, the prescribed treatment with oral hypoglycemic agents were continued. Two patients had HbA1c >7.5%, frequent cases of acetonuria and significant weight loss. C-peptide were declining progressively during 1-year follow up. That's why the diagnosis was changed to DPK A−β−, and lifelong insulinotherapy were prescribed.
Conclusions
Current Aβ classification of DPK is thought to allow to determine necessity of year-long insulinotherapy, which were not proved in our pilot study. The more clinical experience is needed to make strict follow up and treatment recommendations for patients with atypical diabetes.

DOI: 10.1530/endoabs.37.EP374

EP375

Evaluation of quality indicators in hospital discharge reports in diabetic patients from an Internal Medicine Service: are we doing a good clinical practice?

José M Varela-Aguilar[1,2], Rafael Terán-Redondo[1], Maria Luz Calero-Bernal[1], Ana Calzada-Valle[1], Rosa García-Contreras[1], Estefanía Pereira-Díaz[1], Fidel Moreno-Verdejo[1], Francisco Ruiz-Ruiz[1] & Enrique Calderón-Sandubete[1,2]
[1]Internal Medicine Service. Virgen del Rocio Hospital, Seville, Spain; [2]CIBER de Epidemiología y Salud Pública, Seville, Spain.

Spanish Scientific Societies involved in diabetic patient care produced a consensus document with recommendations and quality indicators for hospital discharge reports (HDR).
Objective
To analyse adequacy of HDR in diabetic patients from an Internal Medicine Service according to these recommendations (*Med Clin* (Bar) 2012 **138** 666.e1–666.e10).
Methods
Study based on a programme continuity of care among Primary Care and Internal Medicine Service. We analyse 150 consecutive HDR in diabetic patients from an internal medicine service of a tertiary hospital. HDR were identified by hospital database and five cases were excluded by death. Clinical information was revised according to nine items recommended in document consensus.
Results
Average age 73.5 years, men 47% and women 53%.T2D 96%, 2% T1D, and steroid diabetes 2%. Diabetes *de novo* was present in five cases (3.4%). Time evolution diabetes was recorded in 27% of HDR and HbA1c only in 17.8%. Renal function (MDRD-4): Normal FGR 26.8%, 18.5% CKD stage 2, stage 3 33.5%, stage 4 15.7%, and stage 5 5.5%; however, FGR only was recorded in 9% HDR. Antidiabetic treatment preadmission was not collected in 36.3%. Where it was present were: monotherapy oral antidiabetic agents (OAA) 26.7%, 8.9% combination OAA, OAA more insulin 9.5%, alone insulin 18.6%. At discharge changes were made in the treatment at 35% but only 23.2% consisted justification at HDR. Changes were: first insulinisation 19.8%, OAA substitution 7.5%, and replacing insulin type 7.7%. The 45% of HDR collected recommendations on diet and exercise, glycaemic control targets in 7.5%, other control cardiovascular risk factors 9.5%, periodicity 13% glycaemic control and medical supervision (within review and assistance level) 11%.
Conclusions
Quality of HDR diabetic patients is low compared with the established recommendations. An improvement program should be introduced to optimise and tailor treatment in diabetic patients at hospital discharge.

DOI: 10.1530/endoabs.37.EP375

EP376

Gonadal hormone regulates the expression MATE1 and OCT2 in type 2 diabetes mice

Ligen Ai, Dandan Zhang, Wolin Hou, Junxi Lu, Junling Tang, Huijuan Lu, Taishan Zheng & Fang Liu
Department of Endocrinology and Metabolism, Shanghai Clinical Medical Center of Diabetes, Shanghai Key Clinical Center of Metabolic Diseases, Shanghai Jiao-Tong University Affiliated Sixth People's Hospital, Shanghai, China.

Background and aims
Multi-drug and toxin extrusion 1 (MATE1) and organic cation transporters 2 (OCT2) are important proteins of metformin transport and excretion in liver and kidney. Our previous study showed that there were gender difference of metformin's hypoglycaemic effect and it was independently linked with the oestrogen and testosterone levels in type 2 diabetes patients. This study was designed to observe the impact of oestrogen and androgen on the renal expression of MATE1 and OCT2 in female and male *db/db* diabetic mice.
Materials and methods
Eight week-old *db/db* and their normal control mice were divided into hormone intervention group ($n=20$) which were injected testosterone 10 mg/kg per day ($n=10$) or oestradiol 1 mg/kg per day ($n=10$) for 7 consecutive days, and control group ($n=10$) received the same volume of olive oil for 7 days. Both the intervention group included male subgroup ($n=10$) and female subgroup ($n=10$), respectively, and also had normal control group ($n=5$). The blood were collected to detect plasma testosterone or oestradiol levels at day 7, the RNA and protein were extracted from kidney tissue to detect the expression of MATE1 protein and *OCT2* mRNA and protein with western blot and real-time PCR.
Results
i) After treatment with exogenous hormones, plasma levels of oestrogen (6.2 ± 1.3 vs 5.0 ± 0.94) and androgen (92 ± 23 vs 64 ± 9) increased markedly in both male and female mice ($P<0.01$). ii) Renal *OCT2* mRNA levels in testosterone-treated male (TM) and female (TF) mice were significantly higher than control female mice (CF, 2.6 ± 3.78, $P<0.05$). On the contrary, treatment with oestrogen in both of males (EM) and females (EF) had no significant impact on *OCT2* mRNA expression (both $P>0.05$). Simultaneously, the *MATE1* mRNA levels in testosterone-treated male group increased significantly compared to control male mice(CM, $P<0.05$) and oestrogen-treated male mice ($P<0.05$). No obvious changes of *MATE1* mRNA levels were found in both EM and EF ($P>0.05$). iii) The expression of OCT2 protein in TF was significantly higher than that of CF ($P<0.05$). However, the expression of both the MATE1 and OCT2 protein levels in TM group were higher markedly compared to CM ($P<0.05$). In oestrogen-treated males, the MATE1 expression elevated significantly ($P<0.05$), but the OCT2 expression had no apparent change ($P>0.05$).
Conclusions
Oestrogen and androgen up-regulate MATE1 expression of kidney in male diabetic mice, but have little effect on that of female mice; androgen increases OCT2 expression both in male and female mice, but oestrogen has little effect on their OCT2 expression.
Disclosure
This study was supported by grant from National Natural Science Foundation of China (81070650 for F Liu).

DOI: 10.1530/endoabs.37.EP376

EP377

The clinical effectiveness of screening for gestational diabetes mellitus in primary vs secondary care: results of a randomised controlled trial

Angela O'Dea[1], Marie Tierney[1], Liam Glynn[1], Andrii Danyliv[1], Louise Carmody[2], Brian McGuire[1], John Newell[1], Eoin Noctor[1] & Fidelma Dunne[1]
[1]National University of Ireland, Galway, Ireland; [2]HSE, Galway, Ireland.

Aims
The aim of this paper is to report on the outcomes of a clinical trial investigating the clinical effectiveness of universal screening for gestational diabetes mellitus (GDM) in primary care vs secondary care.
Design and methods
A parallel group randomised controlled trial of universal screening for GDM in primary vs secondary care. The primary outcome – uptake of screening in primary vs secondary care is reported elsewhere. In this article we report on the secondary outcomes of the trial: i) GDM prevalence, ii) timing of screening, iii) time to access antenatal diabetes care, and iv) maternal and neonatal outcomes.
Results
The prevalence of GDM was similar in primary care and secondary care screening groups, and groups were comparable in terms of the timeliness of screening, with both groups receiving screening at a mean of ~26 weeks. However there was a considerable delay (in both groups) in the time to access hospital treatment for women with GDM. For patients screened in the hospital the delay is 19 days, for those screened at the GP the delay is 24 days. Further research is needed to understand the reasons for this delay. In addition the GP group had a higher proportion of large for gestational age infants than the hospital group. It is possible that the delay in access to care is implicated in the increased infant size in this group; further research on a larger sample will be needed to answer this question. There were no differences between groups in maternal outcomes.
Conclusions
The evidence presented in this paper, shows that the hospital is still the best option for GDM screening, in terms of access to screening and in terms of time to access hospital care for those with GDM. Implications for long term GDM care are discussed.
Disclosure
This work was funded by the Health Research Board of Ireland – Interdisciplinary Capacity Enhancement grant number: ICE/2011/3.

DOI: 10.1530/endoabs.37.EP377

EP378

Risks of having gestational diabetes in the future for mothers and their offspring

Sabin Goktas Aydin[4], Ayse Kubat Uzum[1], Banu Kucukemre Aydin[2], Seyda Ozel Yildiz[3], Selda Gedik[1], Cemile Idiz[1], Bülent Canbaz[1], Firdevs Bas[2], Ruveyde Bundak[2] & Nevin Dinccag[1]
[1]Endocrinology and Metabolism Division, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey; [2]Paediatric Endocrinology and Metabolism Division, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey; [3]Biostatistics Department, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey; [4]Department of Internal Medicine, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey.

Introduction
Gestational diabetes (GDM) has an important short and long-term health consequences for both the mother and her offspring. The aim of this study was to evaluate current metabolic status of women with GDM history and their offspring approximately at 10th year after delivery.
Methods
24 mothers who had GDM 10 years before (mean age 41.08 ± 4.13 years and BMI 30.3 ± 5.9) and their children (11 females, 13 males; mean age of 11.0 ± 1.9 years) were enrolled into the study. To evaluate current metabolic status of mothers, 75 g OGTT was performed and according to ADA criteria they were classified into two groups as normal glucose tolerance (group 1: NGT) and glucose intolerance (group 2: IGT and/or DM). Outcomes of foetal determinants were recorded and current clinical status and laboratory features of offspring were checked and evaluated if there would be any associations with mothers' metabolic status.
Results
41.6% of mothers had any degree of glucose intolerance at 10th year after delivery. As we concluded foetal determinants in groups, measurements of birth weight (g), length (cm) were found as 3625.6 ± 680 vs 3197.6 ± 608; 147.6 ± 11.5 vs 146.7 ± 13.0 respectively. As we considered daily status of children, their BMI and waist circumferences were observed as 18.4 ± 3.1 kg/m^2 vs 20.6 ± 5.7 kg/m^2 and 67.7 ± 12.2 cm vs 71.9 ± 10.1 cm respectively ($P>0.05$). Although the difference was not significant, waist circumference and central obesity of offspring in group 2 was found higher. Also results of fasting glucose and insulin levels of children in group 2 were higher than the others; but difference was not statistically significant. Five of them had lipid profile changes.
Conclusion
Frequency of glucose intolerance may be increased in the follow-up years; offspring of mothers having prediabetes may have great risk for obesity and insulin resistance in the future; especially at pubertal period. Those adolescents should be identified and efforts should be done to prevent development of metabolic syndrome and lifestyle should be planned to preserve beta cell function of the pancreas before puberty.
DOI: 10.1530/endoabs.37.EP378

EP379

Maintenance of risk reduction during 3-year follow up in prevention of type 2 diabetes by lifestyle intervention in primary health care setting: Diabetes in Europe Prevention using Lifestyle, physical Activity and Nutritional intervention (DE-PLAN) project

Aleksandra Gilis-Januszewska[1], Beata Piwonska-Solska[1], Zbigniew Szybinski[1], Katarzyna Kissimova-Skarbek[2], Roman Topor-Madry[2], Grzegorz Glab[5], Jaana Lindstrom[3], Marku Peltonen[3], Peter Schwarz[4], Dorota Pach[1], Jaakko Tuomilehto[3] & Alicja Hubalewska-Dydejczyk[1]
[1]Chair and Department of Endocrinology, Jagiellonian University, Krakow, Poland; [2]Institute of Public Health, Jagiellonian University, Krakow, Poland; [3]Diabetes Prevention Unit, National Institute for Health and Welfare, Helsinki, Finland; [4]Department of Medicine III, Carl Gustav Carus of the Technical University Dresden, Dresden, Germany; [5]Department of Rehabilitation, Faculty of Physiotherapy, University School of Physical Education, Krakow, Poland.

Introduction
Extended up to 20 years follow-up of several randomised control trials showed 34–43% diabetes risk reduction. Real life implementation studies performed worldwide in different settings and populations proved that also non-intensive, low budget lifestyle interventions can be effective. However little is known about long-term results of the translational studies.
Objective
To study the risk factors changes of the DEPLAN non-intensive lifestyle intervention in primary health care setting during 3-year follow up.
Research design and methods
Study participants ($n=114$) with baseline diabetes type 2 risk FINDRISC >14, no diabetes, received ten group lifestyle counselling sessions, six motivation phones, and two letters and physical activity. Measurements performed at 12 months after the initiation of the intervention were repeated after 36 months.
Results
Statistical significant risk reduction at 1 year was maintained at 3 years in weight (82.9 vs 81.6 kg), BMI (31.2 vs 30.1 kg/m^2), serum total cholesterol (5.5 vs 5.4 mmol/l), TG (1.85 vs 1.6 mmol/l ($P<0.09$)), and FINDRISC (18.4 vs 16.2 ($P<0.05$)). After 3 years 6% of participants converted to diabetes, while 56% of baseline IFG and IGT reversed to NGT. Physical activity increase, increased consumption of vegetable and fruit and decreased of saturated fat and change of saturated fat to unsaturated observed at one year were also maintained during follow up ($P<0.05$).
Conclusions
Diabetes type 2 prevention through non intensive, real life lifestyle intervention with modest weight reduction is feasible in a primary health care setting and can be maintained during long time observation.

DOI: 10.1530/endoabs.37.EP379

EP380

Discrepancies between the HbA1c criteria and glucose-based criteria for diagnosis of diabetes and pre-diabetes

Raj Kumar Shrestha[1], Prabin Gyawali[2], Eans Tara Tuladhar[1], Vijay Kumar Sharma[1], Sweta Shrestha[1] & Bharat Jha[1]
[1]Department of Biochemistry, Institute of Medicine, Tribhuvan University Teaching Hospital, Kathmandu, Nepal; [2]Department of Clinical Biochemistry, Dhulikhel Hospital, Kathmandu University Hospital, Dhulikhel, Nepal.

The number of the people with type 2 diabetes is increasing globally, therefore there is an increasing need to identify diabetes earlier and more efficiently. Nearly 80% of people with diabetes live in low and middle income countries (LMICs). Traditionally, we have relied on glucose-based criteria (fasting, postprandial, and random) to make the diagnosis of diabetes; however, HbA1c has recently been endorsed as a diagnostic test, as superior alternative to glucose-based criteria. It is still controversy about implementation of HbA1c criteria in LMICs especially due to several cons one of them being high cost. Previous studies have suggested that some degree of discrepancies exist between the HbA1c and glucose based criteria and may vary by race, ethnicity, sex, and age in various populations. Hence, we aimed to access the discrepancies between the new HbA1c-based criteria over glucose-based criteria for diagnosis of diabetes and pre-diabetes among clinically diagnosed Nepalese population. A total of 1277 clinically suspected type 2 diabetes and prediabetes, who attended Tribhuvan University Teaching Hospital (TUTH), Kathmandu, Nepal between January 2012 and April 2014 were recruited in the study. Initial screening was carried out using the FINDRISC questionnaire. The American Diabetes Association (ADA)-glucose based and ADA-HbA1c criterions were used to diagnose diabetes and pre-diabetes. The discrepancies between two criteria to diagnose pre-diabetes and diabetes were evaluated. Significant discordance exists between the HbA1c- and glucose-based criteria for diagnosis of diabetes in Nepalese population. Furthermore, the substantial numbers of subjects with pre-diabetes were missed by HbA1c criterion.

DOI: 10.1530/endoabs.37.EP380

EP381

The correlation of serum ferritin and diabetes, glucose control or insulin resistance, related or not?

Jiang Li, Cheng Xiao & Yongtong Cao
China-Japan Friendship Hospital, Beijing, China.

Background
We have previously investigated the association between serum ferritin levels and risks of metabolic syndrome (MetS) using the same database from 2009 wave of the China Health and Nutrition Survey (2009 CHNS). We confirmed that MetS components are associated with increased serum ferritin levels in both men and women group, included abdominal obesity, hypertriglyceridemia, low HDL cholesterol, high blood pressure, and abnormal glucose level. Although, the prevalence of anaemia was not associated with having diabetes, the anaemic participants have abnormal iron metabolism. This will influence the serum ferritin level. So in this study, we aimed to further investigate the association between serum ferritin concentrations with diabetes, glucose control and IR adjusted for other confounders in non-anaemic Chinese population, especially adjusted other MetS components in multivariable logistic regression analyses.
Methods
Fasting blood samples and anthropometric data collected on 7362 adults aged 18 and older in 2009 wave of the China Health and Nutrition Survey (2009 CHNS). Data were collected by trained physicians. The fasting serum glucose and blood routine examination were measured at local hospitals. Other biochemical markers were analyzed by an automatic clinical chemistry analyser at the Department of Laboratory Medicine of CJFH.
Results
For both men and women, higher concentrations of serum ferritin were associated with higher values for markers of insulin resistance. But after adjusted for age, and some of MetS components, the difference became weak.
Conclusion
We observed a weak association between serum ferritin levels and the prevalence of diabetes and IR in non-anaemic population. Additional studies are needed to elucidate the mechanisms of serum ferritin and risks of diabetes. This may help to reduce diabetes or pro-diabetes.

DOI: 10.1530/endoabs.37.EP381

EP382

Impact of *ACE* gene polymorphism on preeclampsia development and insulin resistance aggravation in pregnant women with type 1 diabetes mellitus

Andriy Hrybanov[1,3], Zoya Rossokha[2] & Tatiana Avramenko[1]
[1]State Institution 'Institute of Pediatrics, Obstetrics and Gynecology by The Academy of Medical Sciences of Ukraine', Kiev, Ukraine; [2]State Institution 'Reference-centre for molecular diagnostics by The Ministry of Public Health of Ukraine', Kiev, Ukraine; [3]Maternity Hospital #2, Nikolayev, Ukraine.

Type 1 diabetes mellitus (T1DM) and preeclampsia (PE) in pregnant women share common pathophysiological pattern (hypovolemia, increased vascular resistance, and kidney damage) and both are genetically determined. Genetic impact on PE development and aggravation of insulin resistance in T1DM pregnant women has been underinvestigated. Thus, the aim of this case-control study was to evaluate the influence of *ACE* gene *I/D* polymorphism on risk of PE and insulin resistance development.
Materials and methods
Inclusion criteria were as following: for group I – T1DM with superimposed PE (30 patients) and for group II – DM without PE (30 patients). Standard examination was undertaken during pregnancy and postpartum, as well as detection of *ACE* gene polymorphism with allele-specific PCR. The obtained results were analysed using STATISTICA 10.0 Software.
Results
Patients of group II had significantly higher prevalence ($\chi^2=10.35$; $P<0.01$) of *II* genotype compared to group I (56.7 and 16.7% respectively) supporting the

protective effect of *II* genotype on PE development in the investigated population (OR = 0.15; 95% CI 0.05–0.51). Fasting lucose levels (*per se* and in relation to different genotypes) didn't differ between both groups before PE appearance, as well as prior to delivery. But in group I we detected elevated glucose levels depending on genotypes: 8.72 ± 1.26 mmol/l – in patients with *DD* genotype, 8.72 ± 1.26 mmol/l – in patients with *ID* genotype, 5.93 ± 0.52 mmol/l – in women *II* genotype. In group I differences in glucose levels reported in patients with *II* genotype compared to patients with *DD* and *ID* genotypes were found to be statistically significant ($P < 0.05$). Other parameters supporting deeper insulin resistance aggravation have been identified prior to delivery only among patients of group I with *DD* and *ID* genotypes.

Conclusion

ACE gene polymorphism determines the risk of PE in pregnant women with T1DM and modulates unfavourable course of the disease, particularly, aggravation of insulin resistance in patients with *DD* and *ID* genotypes.

DOI: 10.1530/endoabs.37.EP382

EP383

Mechanisms of development of carbohydrate metabolism disturbances in acromegalic patients depending on treatment

Alexander V Dreval[1], Irina V Trigolosova[1], Anna V Vinogradova[1] & Bruce H R Wolffenbuttel[2]
[1]Moscow Regional Clinical Research State Institute named after M.F. Vladimirsky, Moscow, Russia; [2]Department of Endocrinology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

Background

In acromegaly, carbohydrate metabolism disorders (CMD) are frequently observed. The effect of therapy of acromegaly on pathogenesis of CMD is not clear.

Aim

To assess the effect of somatostatin analogues (SSA) on pathogenesis of carbohydrate metabolism disturbance in acromegaly.

Patients and methods

103 acromegaly patients were examined (31 men, 72 women; age 54 (46–61) years; 60 had newly diagnosed acromegaly (NA), 23 receiving SSA, 20 after transsphenoidal surgery (TSS). We analyzed fasting plasma insulin and glucose levels (FPI and FPG), HbA1c, the Matsuda, and HOMA-IR indices, area under insulin curve in the first 30 min (AUCins.30) and from 30 to 120 min of oral glucose tolerance test (AUCins.30–120). In 23 NA patients we assessed these parameters after 3 and 6 months of SSA therapy (12 patients) and TSS (11 patients).

Results

The prevalence of CMD in NA, SSA, and TSS groups was 52, 87, and 35% respectively. Levels of HOMA-IR index and FPI did not differ between SSA and TSS groups, but were considerably lower compared to the NA group (HOMA-IR 1.7 (IQR 0.7–3.1) vs 3.3 (2.0–7.4), $P = 0.008$; FPI 46.0 (IQR 17.1–88.00) vs 90.0 (55.3–179.5) mU/l, $P = 0.002$). Early insulin secretion estimated by AUCins.30 was severely reduced in the SSA group compared to the NA and TSS groups ($P < 0.01$). Among 12 prospective SSA-treated patients, the reduction of IGF1 after 6 months coincided with a decrease of FPI and HOMA-IR (both $P < 0.05$), and an increase of the Matsuda index ($P = 0.068$). SSA-treatment resulted in a considerable reduction of early insulin secretion (AUCins.30) during an OGTT compared to the TSS group, while the reduction of AUCins.30–120 was similar between these groups.

Conclusions

Despite reduction of IGF1 levels and insulin resistance during SSA therapy and after TSS, the decrease of early insulin secretion on SSA therapy leads to the development of CMD.

DOI: 10.1530/endoabs.37.EP383

EP384

TRAIL downregulates endothelin 1 and upregulates superoxide dismutase 1 in human aortic endothelial cells under pro-atherorgenic conditions

Hannah Forde[1,2], Colin Davenport[1], Diarmuid Smith[1] & Phil Cummins[2]
[1]Beaumont Hospital, Beaumont, Dublin 9, Ireland; [2]Dublin City University, Glasnevin, Dublin 9, Ireland.

Introduction

Increased oxidative stress is associated with endothelial dysfunction in atherosclerosis and cardiovascular diseases (CVD). Evidence suggests that tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), a member of the tumour necrosis factor (TNF) superfamily, may also be involved in the pathogenesis of CVD. Observational studies have demonstrated that serum levels of TRAIL are inversely correlated with severity of coronary artery disease. This concurs with other recent *in vivo* findings suggesting that TRAIL may exhibit vasoprotective effects towards the endothelium, although the mechanism of TRAIL-mediated vasoprotection remains poorly understood. The aim of this study therefore was to characterise the effect of TRAIL on inflammatory gene expression from vascular endothelial cells *in vitro* under oscillatory flow, an essential component of atherosclerotic plaque formation.

Methods

Primary-derived human aortic endothelial cells (HAECs) were exposed to pathological oscillatory shear stress (± 10 dyns/cm^3) using the IBIDI$_R$ μslide perfusion unit in the presence and absence of recombinant human TRAIL (100 ng/ml, 24 h). RNA was isolated from the cells using a modified Mirvana method. Gene expression was assessed by a PCR array using qPCR.

Results

TRAIL downregulated expression of endothelin 1 (*EDN1*) gene, which encodes the proinflammatory cytokine EDN1. EDN1 is also associated with reactive oxygen species formation. TRAIL upregulated expression of superoxide dismutase 1 (*SOD*) gene, which encodes the potent antioxidant enzyme SOD1.

Conclusion

TRAIL exerts an anti-inflammatory effect on the endotheium under pro-atherogenic conditions, at least in part through reduction of oxidative stress.

Disclosure

This work was supported by the Basic Science Grant, received from the Irish Endocrine Society November 2013.

DOI: 10.1530/endoabs.37.EP384

EP385

Surgical trauma and insulin resistance

Snezana Polovina[1], Dusan Micic[2], Zlatibor Loncar[2], Mirjana Sumarac-Dumanovic[1], Predrag Savic[2], Goran Cvijovic[1], Vladimir Resanovic[2], Svetlana Zoric[1], Danica Stamenkovic-Pejkovic[1], Vladimir Djukic[2] & Dragan Micic[1]
[1]Clinic for Endocrinology, Diabetes and Diseases of Metabolism, Clinical Center of Serbia, Belgrade, Serbia; [2]Emergency Center, Clinical Center of Serbia, Belgrade, Serbia.

Introduction

Different surgical procedures are followed by alteration in insulin sensitivity. The aim of our investigation was to analysed the influence of major (open cholecystectomy) and minor surgical stress (laparoscopic cholecystectomy) on insulin resistance.

Methods

Insulin resistance was calculated by HOMA-IR before surgery and at 1st, 3rd, and 7th day after the elective operations. All participants were divided in two groups: group A with open cholecystectomy $n = 20$; 38.8 ± 4.3 years of age; mean BMI 26.9 ± 1.6 kg/m^2 and group B with laparoscopic cholecystectomy; $n = 20$; 39.8 ± 4.5 years of age; mean BMI 26.8 ± 1.9 kg/m^2.

Results

There were no difference in HOMA-IR between groups A and B before surgery (mean 2.5 ± 0.33 vs 1.99 ± 0.70; $P > 0.05$) as well as the 1st day after surgery (2.55 ± 0.62 vs 1.85 ± 0.58; $P > 0.05$). HOMA-IR was higher in group B 3rd day after operation than in group A (7.56 ± 2.34 vs 2.8016 ± 0.78; $P < 0.05$). There were no difference between two groups 7 days after surgery (0.65 ± 0.45 vs 0.74 ± 0.40; $P > 0.05$).

Conclusion

Open and laparoscopic cholecystectomy are followed by transient insulin resistance which become normal a week after the operation. Laparoscopic cholecystectomy less deteriorate insulin sensitivity in response to stress than open approach.

DOI: 10.1530/endoabs.37.EP385

EP386

A case of maternally-inherited diabetes with deafness

Maja Bakula[1], Maja Cavlovic Naglic[1], Miro Bakula[2] & Lea Smircic Duvnjak[1]
[1]Clinical Hospital Merkur, University Clinic Vuk Vrhovac, Zagreb, Croatia; [2]Clinical Hospital Sveti Duh, Zagreb, Croatia.

Introduction
Maternally-inherited diabetes with deafness (MIDD) is a rare form of monogenetic diabetes caused by a point mutation in mitochondrial DNA at a position 3243A > G. The syndrome is characterised by diabetes and sensoneural hearing impairment. Additional clinical features include short stature, cardiomyopathy, myopathy, renal disease, macular dystrophy, and gastrointestinal disease. The majority of patients usually require insulin therapy within 2 years and metformin is probably best avoided because of interference with mitochondrial function. The genetic change is passed down from an affected mother to all her children. However, the clinical phenotype associated with the mutation may be very heterogeneous.
Case report
We present a case of a lean 35-year-old female patient who was diagnosed with diabetes at the age of 29 years, suffering from hearing loss and migraine. She tested negative for anti-islet humoral markers (ICA, anti-GAD, and anti-IA2) and her insulin secretory reserve was partially maintained. Four years after the diagnosis, insulin was introduced to therapy. Bilateral neurosensory hearing loss was diagnosed at the age of 29 and required the use of hearing aid. There is a family history of diabetes affecting her mother, maternal uncle, and grandmother. The clinical suspicion of MIDD was confirmed by the detection of mitochondrial DNA mutation m.3243A > G in patient's urinary epithelial cell DNA sample.
Conclusion
It is assumed that MIDD affects up to 1% of all patients with diabetes but often goes unrecognised and is misdiagnosed as either type 1 or type 2 diabetes. Although, it is not possible to predict the likely clinical course associated with this mutation due to variation in phenotype, it is important to suspect and confirm the diagnosis by the genetic testing in order to treat the patient optimally, to screen the patient for other clinical features of the syndrome and to look for the affected family members.

DOI: 10.1530/endoabs.37.EP386

EP387

Association of neutrophil to lymphocyte ratio with different glucose metabolism status

Betül Ekiz Bilir[1], Neslihan Soysal Atile[1], Bülent Bilir[2], Birol Topçu[3], Sonat Pınar Kara[2], Derya Baykiz[4] & Murat Aydin[5]
[1]Tekirdag State Hospital, Tekirdag, Turkey; [2]Internal Medicine Department, Namik Kemal University, Tekirdag, Turkey; [3]Biostatistics Department, Namik Kemal University, Tekirdag, Turkey; [4]Cardiology Department, Tekirdag State Hospital, Tekirdag, Turkey; [5]Biochemistry Department, Namik Kemal University, Tekirdag, Turkey.

Introduction
Several studies have shown that prediabetic patients had increased concentrations of inflammatory markers and this association is independent of underlying obesity. Netrophil to lymphocyte ratio (NLR) is considered as a new inflammatory marker and has been studied extensively in a variety of clinical conditions especially in solid tumours and cardiovascular diseases. Studies evaluating the subclinical inflammation in prediabetes revealed positive association of some inflammatory markers with hyperglycaemia. The aim of this study is to evaluate the association of NLR with different glucose metabolism status groups.
Methods/design
The study included 259 patients (213 females, 46 males; mean age 47.4 ± 11.5 and 48.8 ± 15.7 respectively) who admitted to an Out-Patient Endocrinology Clinic of a State Hospital in Turkey. The asymptomatic adults were classified in three groups as normal glucose metabolism, impaired fasting glucose, and impaired glucose tolerance according to 75 g-oral glucose tolerance test. The patients who had diabetes, any thyroid dysfunction, malignancy, pregnancy, any acute or chronic infectious or inflammatory disease, or patients who were on oral anti-diabetic drugs were excluded from the study. BMIs of patients, serum fasting glucose and insulin levels, lipid parameters and complete blood counts with differentials were registered.
Results
There were statistically significant differences between groups in terms of fasting glucose and HOMA-IR levels as expected ($P = 0.000$ and $P = 0.047$ respectively). Otherwise there are no differences in terms of BMI, insulin, lipids, and NLR.

Groups	Age	BMI	Glucose	Insulin	HOMA-IR	TG	HDL	LDL	NLR
Normal ($n = 53$)	42.2 ± 13.9	34.7 ± 7.1	93.9 ± 7.3	11.6 ± 6.9	2.7 ± 1.6	152 ± 97	48 ± 14	136 ± 31	1.86 ± 0.67
IFG ($n = 120$)	48.7 ± 11.1	34.6 ± 7	106.8 ± 7	12.9 ± 6.5	3.4 ± 1.7	160 ± 90	44 ± 13	138 ± 39	1.8 ± 0.61
IGT ($n = 86$)	49.5 ± 12.3	35.9 ± 8	107.6 ± 8.1	13.7 ± 7.3	3.7 ± 2.1	178 ± 106	45 ± 12	133 ± 36	1.85 ± 0.76

Conclusion
Glucose metabolism status was not associated with NLR in our small study cohort. Studies based on a wider population might give a different result in this manner.

DOI: 10.1530/endoabs.37.EP387

EP388

Contribution of glucose variability to HbA1c levels in patients with type 1 diabetes

Luis Cardoso[1], Carla Batista[1], Dírcea Rodrigues[1,2], Carolina Moreno[1,2], Daniela Guelho[1], Nuno Vicente[1], Margarida Balsa[3], Diana Martins[1], Diana Oliveira[1] & Francisco Carrilho[1]
[1]Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; [2]Faculty of Medicine, University of Coimbra, Coimbra, Portugal; [3]Department of Endocrinology, Centro Hospitalar do Baixo Vouga, Aveiro, Portugal.

Background
Optimal management of type 1 diabetes requires full understanding of the relationships between the triad: HbA1c, fasting plasma glucose, and glucose variability (GV). As GV may contribute to HbA1c we assessed the influence of GV in HbA1c levels.
Research design and methods
We retrospectively analysed 9393 h of continuous glucose monitorings (CGMs) from 61 patients with type 1 diabetes. Periods of 24 h with missing values were excluded. We calculated various measures of GV and used a regression model to determine the impact of each GV measure to HbA1c level. GV was calculated using EasyGV Software and CGMs were recorded using iPro2 (Medtronic, Northridge, CA, USA).
Results
A total of 9393 h of CGM were analysed. Mean duration of diabetes was 17.7 ± 9.6 years and HbA1c was 7.9 ± 1.1%. S.D., continuous overlapping net glycaemic action (CONGA), mean absolute glucose (MAG), and mean of daily differences (MODD), were positively correlated with HbA1c (correlation coefficient of 0.26, 0.37, 0.26, and 0.33, respectively, all $P < 0.05$), and all measures of GV were significantly higher for higher values of HbA1c (<7, 7–8, 8–9, and >9%, all $P < 0.05$). Intraday GV measures contributed to 4–16% of HbA1c (S.D.: 10.2%, CONGA: 15.7%, mean amplitude of glycemic excursions (MAGE–CGM) 3.9%, and MAG 8.1%, $P < 0.05$). Interday variability, measured by MODD, accounted for 13.1% of HbA1c. Furthermore, MODD was positively correlated with measures of quality of glycemic control, like glycemic risk assessment in diabetes equation (GRADE) score, J-index, high blood glucose index (HBGI), *M*-value, and average daily risk ratio (ADDR) (correlation coefficient of 0.41, 0.54, 0.57, 0.54, and 0.80, respectively, all $P < 0.05$).
Conclusion
GV contributes significantly to HbA1c levels. This effect is more pronounced at higher HbA1c levels. Interday variability was the most important contributor to HbA1c. GV impairs significantly the quality of glycemic control of type 1 diabetic patients.

DOI: 10.1530/endoabs.37.EP388

EP389

Increasing NAD^+ availability in skeletal muscle to augment energy metabolism

Rachel Fletcher, Craig Doig, Agnieszka Zielinska, Aliesha Griffin, Andrew Philp & Gareth Lavery
University of Birmingham, Birmingham, UK.

NAD^+, an essential coenzyme in energy production, has recently risen to prominence as a signalling molecule central in mediating cellular metabolism and mitochondrial function. NAD^+ dependent protein deacetylase sirtuin (SIRT) proteins regulate key metabolic transcription factors, including FOXOs and PGC-1α in muscle, in response to cellular energy demands and metabolic stress. Declining NAD^+, metabolic and mitochondrial function are hallmark features of many patho-physiological processes such as ageing and type 2 diabetes. Thus, boosting NAD^+ availability may have beneficial and therapeutic potential. NAD^+ consumption (e.g. SIRTS) requires its re-synthesis through precursor salvage to maintain appropriate levels. Here we further define a skeletal muscle specific pathway to NAD^+ and energy metabolism. Through mRNA and protein expression analysis of NAD^+ biosynthesis genes we show that skeletal muscle relies on a limited set of salvage enzymes for NAD^+ biosynthesis and replenishment. The most highly expressed and skeletal muscle specific of which is nicotinamide riboside kinase 2 (Nmrk2), which salvages the NAD^+ precursor molecule nicotinamide riboside (NR) to produce NAD^+. Nmrk2 demonstrates muscle fibre type specificity, being fivefold enriched in type II fibres compared to type I. Nmrk2 expression is induced during mouse myotube differentiation and embryonic muscle development in zebrafish. Primary derived mouse muscle cells supplemented with 0.5 mM NR for 24 h showed a significant 30% increase ($P<0.001$) in NAD^+ levels with unchanged NADH, suggesting a shift in the redox ratio in favour of the oxidised form. Moreover, oxygen consumption rate was increased by 20% in NR treated myotubes when assessed using a Seahorse extracellular flux analyser, indicating that the NR is enhancing mitochondrial respiration as a result of boosting cellular NAD^+ availability. Our data provides evidence that Nmrk2 is important for skeletal muscle NAD^+ bioavailability and highlights the therapeutic potential for NR supplementation to target mitochondrial function in skeletal muscle.

Disclosure

This work was supported by the BBSRC David Phillips Fellowship BB/G23468/1 and the Medical Research Council PhD studentship (grant DHAA GAS 0028).

DOI: 10.1530/endoabs.37.EP389

EP390

Prepregnancy care: an opportunity not to be missed

Aoife Egan, Andriy Danyliv, Louise Carmody, Breda Kirwan & Fidelma Dunne
National University of Ireland Galway, Galway, Ireland.

Introduction

Our aim was to evaluate the effectiveness of a regional prepregnancy care (PPC) programme for women with both types 1 and 2 diabetes.

Methods

This prospective cohort study included women with pregestational diabetes attending five antenatal centres in the West of Ireland between January 2006 and December 2013. Comparisons were made between those that did and did not attend the PPC programme. Primary outcomes included composite adverse neonatal outcome (shoulder dystocia, congenital malformation, stillbirth, or neonatal death), macrosomia, caesarean delivery, admission to neonatal care unit, per trimester HbA1c, and prepregnancy folic acid use.

Results

In total 452 women were included, 275 (60.8%) with type 1 diabetes and 177 (39.2%) with type 2 diabetes. PPC was attended by 148 (32.7%) women. Those who attended PPC were older (33.8 versus 31.8 years, $P<0.01$) and a higher proportion used prepregnancy folic acid (96.6% vs 54.9%, $P<0.01$). Mean first trimester HbA1c was lower among those who attended PPC (6.9% vs 7.8%, $P<0.01$), as was the mean second trimester HbA1c (6.6% vs 6.2%, $P<0.01$). There was no significant difference in third trimester HbA1c between groups. Rates of adverse neonatal outcomes were higher in those that did not attend PPC (9.5% vs 4.1%, $P=0.04$). A lower proportion of infants born to women who attended PPC required neonatal unit admission (37.2% vs 48.7%, $P=0.02$). There was no difference in rates of caesarean delivery or macrosomia between groups. Binary logistic regression analysis identified that attendance at PPC independently reduced the odds of a serious adverse neonatal outcome (aOR 0.27, CI 0.09–0.83, $P=0.02$).

Conclusion

These findings suggest that provision of a regional PPC programme confers both an individual and economic benefit and should be available to all women with pregestational diabetes.

Disclosure

This work was supported by the Health Research Board of Ireland.

DOI: 10.1530/endoabs.37.EP390

EP391

Lipoprotein associated phospholipase A2 was not associated with diabetic rethinopathy

Zehra Candan[1], Fatma Dilek Dellal[2], Esranur Ademoglu Dilekci[3], Ziynet Alphan Uc[4], Handan Bekdemir[5], Gonul Koc[6], Cavit Culha[6], Yalcin Aral[6], Guner Uney[6] & Zuleyha Yalniz Akkaya[6]
[1]Ankara Medical Park Hospital, Ankara, Turkey; [2]Ankara Ataturk Training and Research Hospital, Ankara, Turkey; [3]Bitlis State Hospital, Bitlis, Turkey; [4]Usak State Hospital, Usak, Turkey; [5]Izmir Sifa University Hospital, Izmir, Turkey; [6]Ankara Research and Training Hospital, Ankara, Turkey.

Aim

Diabetic rethinopathy is an important microvascular complication in diabetic patients. The association between hyperlipidemia and diabetic rethinopathy remains elusive. Lipoprotein associated phospholipase A2 (Lp-PLA2) is Ca independent serine kinase that hydrolyses oxidized LDL and forms lysilphoshotidylcholine and free fatty acid. The aim of the study was to determine serum levels of Lp-PLA2, traditional lipids, apolipoproteins in patients with diabetic rethinopathy and to evaluate correlation of these parameters with disease severity.

Methods

A total of 67 diabetic patients were divided into three groups (nonproliferative diabetic rethinopathy, proliferative rethinopathy, and no rethinopathy) based on fundoscopic examination and matched to 15 healthy and nondiabetic people. Blood samples for lipids, apolipoproteins, Lp-PLA2 were drawn.

Results

No significant difference was observed in terms of total cholesterol, TG, LDL-C levels between groups. However HDL-C levels were similar in proliferative diabetic rethinopathy, nonproliferative rethinopathy patients and diabetic controls (42.5 ± 6.4, 46.8 ± 12.3) and were lower than healthy controls (61.1 ± 14.5, $P<0.005$). No statistically significant difference was shown with respect to apolipoprotein A1, apolipoprotein B, apo B:apo A1 ratio in all comparisions. Serum levels of Lp-PLA2 was similar in all groups.

Conclusions

Serum levels of lipids, apolipoproteins and Lp-PLA2 were not associated with diabetic rethinopathy. Although, Lp-PLA2 were found to be associated with macrovascular complications of diabetes in most studies, the role of this molecule in microvascular complications wasn't known. The larger sample sized studies may clarify the relationship between Lp-PLA2 and rethinopathy.

DOI: 10.1530/endoabs.37.EP391

EP392

Concentrations of the vitamin D metabolite 1,25(OH)2D and its relationship to inflammatory and metabolic parameters in diabetes type 2

Silvija Canecki-Varzic[1,2], Ivana Prpic-Krizevac[1,2] & Ines Bilic-Curcic[1,2]
[1]Clinical Hospital Center Osijek, Osijek, Croatia; [2]Faculty of Medicine, Josip Juraj Strossmayer University, Osijek, Croatia.

Background

While 25-hydroxy-vitamin D (25(OH)D) has been thoroughly investigated, the role of active vitamin D metabolite $1,25(OH)_2D$ in a metabolic syndrome still remains unclear. The aim of our study was to determine the association between 25(OH)D and $1,25(OH)_2D$ levels and several metabolic parameters and inflammatory markers in postmenopausal women with diabetes type 2 (T2DM).

Methods

Anthropometric variables, serum 25(OH)D, $1,25(OH)_2D$, C-reactive protein (CRP), fibrinogen, PAI-1, fasting glucose, fasting insulin, and HbA1c were measured in 125 postmenopausal women with T2DM. Insulin resistance was estimated by homeostasis model assessment (HOMA-IR) and β-cell function by HOMA-B. A total of 125 diabetic patients were divided by BMI in normal weight group ($n=22$, BMI 22.7 ± 1.5 kg/m^2) and adipose group ($n=93$, BMI 32.2 ± 5.8 kg/m^2). Control group consisted of healthy obese postmenopausal women ($n=46$, BMI 34.9 ± 6 kg/m^2).

Results

Serum 25(OH)D concentrations were highest in the lean diabetics compared with obese diabetics and control subjects ($P<0.0007$) and were significantly associated with fasting glucose, insulin, HOMA-B, BMI, and PAI-1. In diabetic patients 25(OH)D levels were positively associated with HDLC ($P<0.01$) and negatively with triglycerides ($P<0.04$) and PAI-1 ($P<0.001$). Serum $1,25(OH)_2D$ concentrations were significantly higher in control obese subjects (77.4 ± 17.0 nmol/l) compared with adipose diabetics ($P<0.001$), with no difference in relation to lean diabetics. Fasting glucose and HbA1c negatively correlated ($P<0.01$), whereas cholesterol and LDLC positively correlated

($P<0.01$) with 1,25(OH)$_2$D. Furthermore, 25(OH)D correlated with PAI-1 in all subjects while 1,25(OH)$_2$D correlated with fibrinogen but only in obese control subjects.
Conclusions
In T2DM women low serum 25(OH)D and 1,25(OH)$_2$D levels were associated with atherogenic dyslipidemia, glucose parameters, and low grade inflammation. The active hormonal form of vitamin D, 1,25(OH)$_2$D correlated with cholesterol, LDLC, and fibrinogen, while 25(OH)D correlated with triglycerides, HDLC, and PAI-1, suggesting that there may be an independent mechanism of action for 1,25(OH)$_2$D in relation to metabolic dysregulation.

DOI: 10.1530/endoabs.37.EP392

EP393

Abstract unavailable.

DOI: 10.1530/endoabs.37.EP393

EP394

10 years of improving outcomes for women with pre-gestational diabetes

Lisa Owens[1,2], Louise Carmody[1,2], Aoife Egan[1,2] & Fidelma Dunne[1,2]
[1]Galway Diabetes Research Centre, Galway, Ireland; [2]Atlantic Diabetes in Pregnancy Programme, Galway, Ireland.

Pregnancy for women with type 1 or type 2 diabetes is a high-risk time. The Atlantic diabetes in pregnancy (DIP) programme aims to provide coordinated, optimal evidence-based clinical care for women with diabetes over five hospital centres in the West of Ireland. After previously auditing pregnancy outcomes in 2008 and again in 2011 we now look at our 10-year outcomes. Changes in clinical care delivery that have occurred over that time include; the provision of dedicated combined antenatal/diabetes clinics, pre-pregnancy care clinics delivered by specialist diabetes and obstetric staff, use of a diabetes electronic management system, use of locally developed clinical care guidelines and professional and patient education materials. We examined outcomes in 440 pregnancies, divided into groups in groups of pre- and post-audit cycles, after which further change was implemented (2005–2008, 2009–2011, and 2012–2014). We saw a trend towards reduction in a lot of major outcomes. This is despite an increase in maternal age, maternal weight/BMI and a significant increase in numbers of women obese at the start of pregnancy. There has been an overall significant reduction in gestational weight gain. There has not however been a reduction amongst overweight women, just obese and normal weight women. We also saw an increase in attendance at pre-pregnancy care and a reduction in mean HbA1c values. There has been a significant reduction in congenital malformations and a non-significant reduction in large for gestational age babies, birth weight, smoking, neonatal hypoglycaemia, jaundice and admissions to the neonatal intensive care unit.
Conclusion
Changing the process of clinical care delivery can improve outcomes in women with pregestational diabetes. We now need to target women prior to pregnancy in order to optimise BMI.
Disclosure
Health Research Board of Ireland.

DOI: 10.1530/endoabs.37.EP394

EP395

Unawareness hypoglycaemia in patients with type 1 diabetes mellitus: prevalence and predictive clinical characteristics

Mariola Méndez Muros, Eyveé Arturo Cuéllar Llocl la, Fernando García Pérez, Guillermo Martínez de Pinillos Gordillo, Mariana Tomé Fernández-Ladreda, Juan Manuel Garcíade Quirós Muñoz, José Ignacio Fernández Peña, José Ignacio Fernández López, Margarita Rivas Fernández, Juana Magdalena Hidalgo Amat, Santiago Durán García & María Victoria Cózar León
Valme University Hospital, Seville, Spain.

Background
The prevalence of unawareness hypoglycaemia in patients with type 1 diabetes mellitus (T1DM) is uncertain. This study aims to determine its prevalence and predictive clinical characteristics with greater precision.
Methods
Prospective study. 128 patients were recruited between September 2013 and January 2014. Awareness of hypoglycaemia was assessed using the 'Clarke' questionnaire and was classified into two groups, depending on the presence (group 1) or absence (group 2) of symptoms perception.
Results
The 'Clarke' questionnaire was completed by 128 patients with T1DM: 53.8% females; mean age 36.2 ± 12.8 years; duration of diabetes 15.65 ± 9.18 years; HbA1c 7.45 ± 1.35%; 87.5% used intensive insulin therapy with multiple insulin doses. 80 patients (62.5%) were included in group 1 and 48 (37.5%) in group 2. The frequency of at least one episode of severe hypoglycaemia during the previous year was 20.3% in group 1 and 37.5% in group 2. 43% of patients in group 1 and 56.3% in group 2 needed a blood glucose value <50 mg/ml to notice symptoms. 43% of patients in group 1 and 66.7% in group 2 considered their symptoms hardly ever or never warned them about the presence of hypoglycaemia. There have not been any significant differences between both groups in diabetic microangiopathy, duration of disease, eating disturbances and insulin regimens (basal-bolus vs biphasic).
Conclusions
We have observed a high prevalence of unawareness hypoglycemia in patients with T1DM. Educational strategies are needed to improve their perception of hypoglycaemia symptoms.

DOI: 10.1530/endoabs.37.EP395

EP396

Glycaemic control is comparable in patients with or without significant hepatic fibrosis as assessed by NAFLD fibrosis score

Jun Liong Chin, Grace Chan, Phyllis Sea-Pui Sin, Zeshan Siddiqui, Eoin O'Rathallaigh, Abdur Rahman Aftab, Garry Courtney & Colm McGurk
St. Luke's General Hospital, Kilkenny, Ireland.

Background and aims
Non-alcohol fatty liver disease (NAFLD) is increasingly recognised in diabetic patients with metabolic syndrome. Patients with poorly-controlled diabetes and metabolic syndrome are likely to have significant liver inflammation leading to fibrosis. NAFLD fibrosis score (NFS) is a validated non-invasive scoring system that identifies liver fibrosis in patients with NAFLD. The aim of this study is to examine the glycaemic control in patients with or without significant hepatic fibrosis as assessed by NFS in routine clinic.
Methods
All patients with type 2 diabetes or impaired glucose tolerance/fasting glucose, attending the diabetic clinic from March to June 2014 were included retrospectively. Patients with type 1 diabetes and gestational diabetes were excluded. Data were obtained from laboratory database and electronic patient record (Cellma). NFS was calculated for each patient based on age, BMI, diabetes, AST/ALT, platelet, and albumin.
Results
521 patients were screened and only 29.4% (153) of patients with complete laboratory data were studied. In our cohort of 153 patients, 64.1% (98) of patients were male and the median age was 63 (IQR 56.0–71.5) years. Using the NAFLD fibrosis score, almost a quarter of our patients (24.2%, $n=37$) had significant fibrosis with a median score of 1.169 (0.898–1.563) while the rest of the patients were indeterminate (66.0%, $n=101$) or had no significant fibrosis (9.8%, $n=15$). The median BMI for patients with significant hepatic fibrosis was 30.0 (27.8–34.5) kg/m^2 while for patients without significant fibrosis (including indeterminate score based on NFS), the median BMI was 34.8 (30.3–43.2) kg/m^2 ($P<0.01$) . Interestingly, there were no significant differences in the mean HbA1c readings in patients with or without significant hepatic fibrosis (55.2 ± 15.3 mmol/mol vs 56.6 ± 17.9 mmol/mol; $P=0.639$).
Conclusion
In conclusion, we did not observe any significant differences in glycaemic control in patients with or without significant hepatic fibrosis, as assessed by NAFLD fibrosis score.

DOI: 10.1530/endoabs.37.EP396

EP397

Targeting optimal metabolic parameters in type 1 diabetes and concomitant coeliac disease: an extra challenge

Clifford Kiat[1], Tom Cotter[1], Sean Dinneen[1,2] & Esther O'Sullivan[1,2]
[1]University Hospital Galway, Galway, Ireland; [2]National University of Ireland, Galway, Ireland.

Patients, especially children, with type 1 diabetes (T1D) have an increased risk of developing other autoimmune disorders including coeliac disease (CD). While the general population prevalence of CD is ~1%, in patients with T1DM the prevalence of CD is higher (0.6–16%). Gluten free diet (GFD) imposes limitations in dietary options. Many of the gluten-free foods have a high glycemic index. This can influence glycemic values and metabolic parameters. We selected the subgroup of pts with T1D attending our service between June 2011 and June 2013 who have concomitant CD ($n=30$). To determine whether differences exist in their metabolic parameters compared to those of the total cohort of patients with T1D attending our service in the same time-period ($n=905$), we did a cross-sectional analysis of clinic measurements of weight, BMI, BP, HbA1c, lipid profiles, albumin creatinine ratios, and tissue transglutamine IgG antibody titres (TTG) (as a marker of adherence to a GFD). The CD+T1D group consisted of 18 (60%) females and 25 (83%) adults (>18 years) and had a mean age of 37 (s.d. 19). The T1D group consisted of 431 (48%) females and 798 (88%) adults (>18 years) and had a mean age of 37 (17). HbA1c in the CD+T1D group was 76.4 mmol/mol (s.d. 17.4) vs 70.3 (17.7) in the T1D group ($P=0.04$). Children overall had higher HbA1c values (83.6 and 75.7, $P<0.05$). In the CD+T1D group, lipid profiles showed lower total cholesterol (4.0 vs 4.6), LDL cholesterol (2.0 vs 2.4), triglycerides (1.0 vs 1.3), and higher HDL cholesterol (2.0 vs 1.7) mmol/l levels than the T1D group ($P<0.003$). There was no significant difference in the proportion taking cholesterol lowering drugs (35% vs 31%). The CD+T1D group had a lower average BMI (24.0 vs 26.4, $P<0.004$). CD+T1D presents a challenge to achieving target HbA1c but confers some benefits for lipid profiles.

DOI: 10.1530/endoabs.37.EP397

EP398

Modulation of metabolic parameters and antioxidant enzymes in diabetic ageing female rat brains: beneficial role of metformin

Pardeep Kumar, R K Kale & N Z Baquer
Jawaharlal Nehru University, New Delhi, India.

Objective
The objective of this study was to investigate beneficial effects of metformin on membrane bound enzymes (monoamine oxidase, Na^+K^+ ATPse) and antioxidant enzymes (sueroxidase dismutase and glutathione *S*-transferases), lipid peroxidation, neurolipofuscin, and DNA degradation in diabetic aging female rats.
Methods
Young (3 months) adult (12 months) and aged (24 months) rats will be diabetic by using alloxan monohydrate. Metformin was administered i.p. at a dose of 200 mg/kg per day for 30 days to both control and diabetic aging rats. Learning was tested in a Morris water maze. A detailed study was carried on membrane linked enzymes, membrane fluidity, neurolipofuscin, antioxidant enzymes, and DNA degradation to identify the antidiabetic and antiaging role of metformin using biochemical, molecular, and histiochemical study.
Results
Present study shows that there was a similar pattern of increased lipid peroxidation, neurolipofuscin, DNA degradation, and monoamine oxidase activity and a decrease in membrane fluidity, Na^+K^+ ATPse, antixodant enzymes activities in both aging and diabetes. Metformin was found to be an effective treatment in stabilizing and normalizing the membrane functions; therefore this therapy can be considered an alternative to be explored further as a means of diabetic and aged related disorders control. Metformin treatment also helped to reverse the age-related changes studied, to normal levels, elucidating an anti-aging, antidiabetic, and neuroprotective action.
Conclusions
The results of this study will be useful for pharmacological modification of the aging process and applying new strategies for control of age-related disorders including metabolic syndrome.
Disclosure
CSIR grant 2005-6.

DOI: 10.1530/endoabs.37.EP398

Diabetes (complications & therapy)

EP399

Obstructive sleep apnoea and type 1 diabetes mellitus

Hiang Leng Tan[1], Feaz Babwah[2], Najeeb Waheed[2] & Muhammad Imran Butt[3]
[1]Weston General Hospital, Weston Super Mare, UK; [2]Hereford County Hospital, Hereford, UK; [3]Peterborough City Hospital, Peterborough, UK.

Introduction
Obstructive sleep apnoea (OSA) is common and frequently found in patients with obesity and type 2 diabetes mellitus. This case report shows the infrequently documented link between OSA and type 1 diabetes and highlights the need to confirm the type of diabetes especially in complex and atypical cases.
Case report
A 44-year-old gentleman, with a BMI of 34, was diagnosed with type 2 diabetes and was treated with metformin and given lifestyle advice. One year later, he became unwell with 2.5 stone weight loss, polyuria, and polydipsia. The history pointed towards a diagnosis of type 1 diabetes and he was commenced on basal bolus insulin regimen. During one of his clinic consultations, he described symptoms of OSA and both Epworth Sleepiness Scale and formal sleep studies performed subsequently confirmed the diagnosis of OSA. Anti-GAD antibody was positive, confirming the diagnosis of latent autoimmune diabetes of adult (LADA), a subset of type 1 diabetes. Metformin was re-initiated and within 6 months, his insulin requirement was reduced by about 50%. He only had minimal weight loss during this period.
Conclusion
There are now studies showing an unexpectedly high prevalence of OSA in type 1 diabetes patients independent of weight and this case serves as a reminder the importance of screening for OSA in this patient group due to its serious implications. Secondly, this patient showed a remarkable reduction in insulin requirement after metformin initiation although he had type 1 diabetes. Most studies showed only an average of 20% insulin sparing effect.

DOI: 10.1530/endoabs.37.EP399

EP400

Efficacy of sitagliptin added on to intensive insulin therapy in type 2 diabetic patients

Bengur Taskiran & Guven Baris Cansu
Yunus Emre State Hospital, Eskisehir, Turkey.

Aim
Despite multiple dose injections some patients still fail achieving HbA1c target. We aimed to evaluate the effect of sitagliptin add on therapy to multiple dose insulin injections.
Method
Data of 47 (seven males and 40 females) type 2 diabetic patients who had HbA1c over 7% were retrospectively evaluated. They were already treated with premix lispro or aspart insulin ($n=28$), glargine plus premeal regular or aspart or lispro insulin ($n=15$), and detemir plus premeal aspart insulin ($n=2$), and glargine plus premix lispro insulin ($n=2$) for at least 3 months before sitagliptin add on therapy. The insulin scheme was intensified (glargine plus premeal regular or aspart or lispro insulin ($n=32$), and detemir plus premeal aspart insulin ($n=2$), and NPH twice daily plus regular or lispro insulin ($n=13$)).
Results
The patients were aged 56.26 ± 8.69 years. Mean duration of diabetes was 14.41 ± 7.57 years. Mean BMI 37.75 ± 6.08 kg/m^2 (28.81–53.78 kg/m^2). One patient had sleeve gastrectomy and still continued sitagliptin afterwards. Duration of insulin therapy before sitagliptin therapy ranged between 3 months and 22 years. Before sitagliptin therapy total daily dose was 91.13 ± 34.22 units (32–204 units) ($n=46$). HbA1c level within 6 months preceding sitagliptin therapy was $9.65\pm1.70\%$ (7.25–14.37%). Duration of sitagliptin therapy ranged between 1 and 25 months. The patients who used sitagliptin <6 months were the ones who were lost follow-up. Neither of them discontinued sitagliptin due to side effects. Weight change was 3.01 (gain) $\pm$ 3.47 kg (-2.30 to 15.00). Only 43 had follow-up total daily insulin dose data. Mean change was 20.72 units increment $\pm$ 29.86 (-48 to 90 units). According to the available follow-up records, mean HbA1c change was $0.95\pm1.48\%$ (-4.32 to 2.58%). When data of the patient who had undergone sleeve gastrectomy was deleted, mean weight change was 2.63 (gain) $\pm$ 2.74 kg (-2.30 to 6.60). Mean total daily insulin dose change was 23.90 units increment $\pm$ 30.68 (-48 to 90 units). Mean HbA1c change did not differ significantly ($0.93\pm1.48\%$; range: -4.32 to 2.58%). HbA1c change was correlated neither with total daily insulin dose change nor with weight change.

Total daily insulin dose change also did not correlate with weight change.
Conclusion
Adding sitagliptin to intensive insulin therapy do not cause consistent significant change in terms of weight change, HbA1c change, and total daily insulin dosage change.

DOI: 10.1530/endoabs.37.EP400

EP401

Abstract withdrawn.

DOI: 10.1530/endoabs.37.EP401

EP402

Is vitamin D a predictor of premature atherosclerosis in type 2 diabetic patients?

Nehal Hammdy[1], Nagwa Abd El Gaffar[2], Randa Abdo[1] & Mary Wadia[1]
[1]Cairo University, Cairo, Egypt; [2]National Research Center, Cairo, Egypt.

Introduction
A poor vitamin D status has been related to an increased risk of cardiovascular disease. Carotid intima–media thickness (IMT) has shown to be an early marker of subclinical atherosclerotic Therefore, we aimed at examining the association between vitamin D status and the extent of carotid IMT in type 2 diabetics.
Subjects and methods
In a cross sectional study 78 type 2 diabetic patients attending the Diabetes and Endocrinology Clinic in Kasr El Ani Hospital were subjected to: full history, physical examination, anthropometric measurements (BMI and waist circumference), fasting glucose, HOMAIR, serum cholesterol, triglycerides, LDL, HDL, 25(OH) vitamin D, and carotid Doppler.
Results
Diabetics with normal CIMT ($n=26$) all with sufficient vitamin D, diabetic with increased CIMT ($n=52$) (40 sufficient 76.9% and 12 insufficient 23.1%). Six patients with increased CIMT had carotid plaque. Only one patient had vitamin D insufficiency, all other five patients had sufficient vitamin D. Vitamin D negatively correlated with Rt IMT, however, not statistically significant ($r=-0.003$, $P=0.981$). Negative correlation between fasting blood glucose and vitamin D statistically significant ($r=-0.415$, $P<0.001$). Negative correlation between cholesterol and Rt intima ($r=-0.340$, $P=0.002$).
Conclusion
Low serum 25(OH)D has no consistent association with mean IMT. Thus could not predict subclinical atherosclerosis in diabetics, the contribution of the local activated vitamin D system within atherosclerotic plaque has not been appropriately investigated yet. Therefore, both basic research studies and clinical trials are needed for better elucidating the therapeutic and path physiological role of vitamin D in atherogenesis and CV diseases.

DOI: 10.1530/endoabs.37.EP402

EP403

Long-term use of insulin pump vs pens in treating young children with type 1 diabetes

Ashraf Soliman[1,2], Fawzia Alkhalaf[1], Mahmoud Alzyoud[1], Noura Alhumaidi[1], Ahmed Elawwa[1,2], Aml Sabt[1], Fawzia Alyafie[1] & Nagwa Aldersy[1]
[1]Hamad Medical Centre, Doha, Qatar; [2]University of Alexandria, Alexandria, Egypt.

Introduction
Unequivocal evidence for the benefit of MDI, the analogs and CSII-treatment in children is lacking. This study assesses the effects of insulin pump (CSII) vs pens in treating children with type 1 diabetes for more than 2 years.
Research design and methods
Diabetes control and anthropometric data of 94 children with type 1 diabetes who were on continuous s.c. insulin therapy using insulin pump were compared with those for 40 children with type 1 diabetes mellitus who were on multiple injections using basal insulin (Lantus) and prandial insulin (Novo-rapid) (three to four shots/day) for more than 2 years. Mean HbA1c, mean blood glucose (MBG), hypoglycemia and DKA frequency were recorded.
Results
Patients using pump therapy were older than patients on pen injections. However, the duration of diabetes did not differ between the two groups. Patients on CSII had significantly lower HbA1c, MBG, and insulin dose/kg compared with children using insulin pens. The frequency of severe hypoglycemia, ketoacidosis, or hospitalization was similar between groups at this time period. The majority (90/94) of patients on CSII expressed their desire to continue on CSII and appreciated its value as easier way to adjust insulin dose to their variable daily requirements.
Discussion
CSII is safe and well tolerated in young children with diabetes and may have positive effects on QOL. In addition, CSII improved diabetes control using less insulin/kg compared with pen injections. However, children on CSII had higher weight gain and BMI.
Conclusion
Our data indicate that CSII is safe and well tolerated in this population. The proper use of CSII in children with type 1 diabetes mellitus appears to improve glycaemic control using less s.c. insulin/kg per day and their quality of life. However, excessive weight gain should be avoided.

DOI: 10.1530/endoabs.37.EP403

EP404

Effect of liraglutide 1.8 mg in patients with non-controlled type 2 diabetes mellitus at an endocrinology clinic: LIED-2 Study

Alvaro J Muriel[1], Alvaro A Herrera[2] & Alin Abreu Lomba[2]
[1]Universidad Libre Cali, Cali, Valle del Cauca, Colombia; [2]Centro Médico Imbanaco, Cali, Valle del Cauca, Colombia.

Background and aims
To describe the characteristics of patients with non-controlled type 2 diabetes mellitus with liraglutide treatment.
Materials and methods
Retrospective descriptive study. 85 outpatients (women 49, ages 18–86 years old with non-controlled type 2 diabetes mellitus were evaluated between July 2013 and March 2014 and received treatment with liraglutide 1.8 mg Q18/day (0.6 mg Q18 during the first week, 1.2 mg Q18 during the send week and 1.8 mg during the third week and the rest of the treatment). Age, sex, diagnosis time, weight, HbA1c, fasting glucose, systolic and diastolic blood pressure, pharmacological treatment during 6 months were extracted for analysis.
Results
Patients treated with liraglutide 1.8 mg as monotherapy or in conjunction with a therapeutic scheme decreased HbA1c values at 3 and 6 months (1.02% 95% CI $\pm$ 0.93 $P<0.0001$ y 2.08% 95% CI $\pm$0.8 $P<0.0001$); fasting glucose at 3 and 6 months (37 mg/dl 95% CI$\pm$33 $P<0.0001$ y 68 mg/dl 95% CI$\pm$26 $P<0.0001$); weight at 3 and 6 months (3 kg 95% CI$\pm$10 $P<0.0001$ y 5 kg 95% CI$\pm$10 $P<0.0001$); SBP at 3 and 6 months (9 mmHg 95% CI$\pm$15 $P<0.0001$ y 16 mmHg 95% CI$\pm$16 $P<0.0001$); DBP at 3 and 6 months (3 mmHg 95% CI$\pm$6 $P<0.0001$ y 6 mmHg 95% CI$\pm$6 $P<0.002$). 40% of patients reached HbA1c <7.0; 20% reduction of HbA1c, 39% reduction in fasting blood glucose, 6% reduction in mean weight (1–18%, 1–12 kg), 95% reached SBP <140 mmHg; 100% reached DBP <90 mmHg. Reported adverse events during treatment were nausea (27%), abdominal pain (18%), hypoglycaemia (14%), diarrhoea (9%), respiratory symptoms (7%). Metformin was present in 65% cases of nausea, 55% cases of diarrhoea and 43% of cases of abdominal pain. No fatal adverse events occurred.
Conclusion
Patients treated with liraglutide 1.8 mgQ18/day in monotherapy or in conjunction with a therapeutic scheme showed a decrease in HbA1c, fasting glucose, weight, SBP, DBP during a 6 month treatment.

DOI: 10.1530/endoabs.37.EP404

EP405

Correlation of left ventricular hypertrophy and left ventricular diastolic dysfunction with HbA1c in newly diagnosed type 2 diabetics

Manish Gutch[1], Syed Mohd Razi[1], Abhinav Gupta[1], Sukriti Kumar[2] & Keshav Gupta[1]
[1]LLRM Medical College, Meerut, India; [2]SGPGI, Lucknow, Uttar Pradesh, India.

Introduction
Diabetes is associated with dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Diabetic macrovascular complications are the leading cause of deaths in diabetics. The correlation between LVH and LVDD with HbA1c is not clear in newly diagnosed T2DM Indian diabetics.
Aims and objective
To study the frequency of left ventricular hypertrophy (LVH) and left ventricular diastolic dysfunction (LVDD) in normotensive newly diagnosed type 2 diabetic patients by using 2D echocardiography and correlation with HbA1c.
Materials and methods
The present study is an observational cross sectional study in which 100 newly diagnosed normotensive type 2 diabetes mellitus patients between 30 and 60 year of age were enrolled from endocrine OPD of a tertiary care centre during a period of 1 year. All cases were subjected to thorough clinical history, examination and 2D echocardiography along with HbA1c.
Observations and results
Out of 100 patients of newly diagnosed normotensive type 2 DM; 41% patients had LVDD and 37% patients had LVH. The mean HbA1c of population with LVDD was $7.67 \pm 0.90\%$ and that with LVH was $7.74 \pm 0.91\%$. The LVDD and LVH were positively correlated with HbA1c (P value $= 0.0057$ and 0.0011) respectively.
Conclusion
LVDD and LVH were positively correlated with HbA1c in newly diagnosed T2DM population.

DOI: 10.1530/endoabs.37.EP405

EP406

The frequency of fall and risk factors in elderly patients with type 2 diabetes

Pelin Tutuncuoglu[2], Fulden Sarac[1], Sumru Savas[1], Asli Kilavuz[3] & Fehmi Akcicek[1]
[1]Department of Geriatrics Medicine, Ege University Medical Faculty, Izmir, Turkey; [2]Department of Endocrinology and Metabolism, Atatürk Training and Research Hospital, Izmir, Turkey; [3]Department of Internal Medicine, Ege University Medical Faculty, Izmir, Turkey.

The aims of the study were to determine the frequency of falls in elderly patients with type 2 diabetes mellitus and to evaluate the risk factors for falls. In the study, 100 (mean age 64.9 ± 11.0 years) (65 females, 35 males) elderly patients with type 2 DM were enrolled. Medical record abstraction of sociodemographic, clinical, and laboratory data was performed retrospectively. Medication characteristics, comorbidities, location and height of fall, associated injuries and outcomes were obtained from patients history with questionnaire-based interviews. A fall was described to patients as 'landing on the floor or ground, or falling and hitting an object like a table or stair.' The frequency of falls found to be 21% in elderly diabetic patients, particularly in women. Mean duration of diabetes was 18.7 ± 3.1 years in elderly who had fall. In this group, neuropathy, retinopathy, nephropathy, stroke, coronary heart disease, arthritis, difficulty with instrumental activities of daily living and lowgrip strength and low walking speed were found to be in 20, 18, 5, 7, 5, 9, 4 and 5 patients respectively. Eleven patients reported using triple oral antidiabetic drug (OAD), three patients reported using OAD and insulin, seven patients reported using only insulin. Sedative treatment was seen in 11 patients. Mean duration of diabetes was 7.9 ± 5.1 years in elderly patients who had no fall. Non-ground level falls (non-GLF) were recorded in six patients. Significantly higher injuries such as hip fracture were found in two patients. Mean levels of fasting and postprandial glucose and HbA1c were found to be 200.1 ± 61.0 and 210.9 ± 43.9 mg/dl and 11.1 ± 0.1, respectively, in elderly patients who had fall. Falls are significant health problem among the diabetic elderly. Non-GLF account for 6% of patients and are associated with chronic diabetic complications, comorbidities, medications, difficulty with instrumental activities of daily living and low grip strength and low walking.

DOI: 10.1530/endoabs.37.EP406

EP407

Factors influencing prognosis in patients hospitalised with diabetic ketoacidosis

Manish Gutch[1], Sukriti Kumar[2], Syed Mohd Razi[1], Abhinav Gupta[1] & Keshav Kumar Gupta[1]
[1]LLRM Medical College, Meerut, Uttar Pradesh, India; [2]SGPGI, Lucknow, Uttar Pradesh, India.

Background
Diabetic ketoacidosis is characterised by biochemical tired of hyperglycemia, acidosis, and ketonemia. It remains a life threatening condition despite improvement in diabetic care, timely identification and intervention remains the backbone of treatment.
Aim and objectives
i) To evaluate the clinical and biochemical prognostic markers in diabetic ketoacidosis. ii) To correlate the various prognostic markers with mortality in diabetic ketoacidosis.
Settings and design
A prospective multicenteric observational study done at tertiary care centre.
Methods and materials
Two hundred and seventy patients hospitalised with diabetic ketoacidosis over a period of 1 year were evaluated clinically and by laboratory tests. Serial assays of serum electrolytes, glucose and blood pH, and clinical outcome of either discharge home or death were evaluated.
Statistical analysis
Data were analysed by SPSS version 17 and were presented in the values of mean, median, and percentages. The P value of < 0.05 was considered significant.
Results
The significant predicators of final outcome obtained were further regressed together and subjected with multivariate logistic regression (MLR) analysis. The MLR analysis further revealed that the male sex had 7.93-fold higher favourable outcome as compared to female sex (OR = 7.93, 95% CI 3.99–13.51) while decrease in mean APACHE II score (14.83) and S. PO_3^- (4.38) at presentation may lead 2.86 (OR = 2.86, 95% CI 1.72–7.03) and 2.71 (OR = 2.71, 95% CI 1.51–6.99) fold better favourable outcome respectively as compared with higher levels (APACHE II score: 25.00; S. PO_3^-: 6.04).
Conclusions
Sex, baseline biochemical parameters like APACHE II score, and phosphate level, were important predicator of mortality from DKA.

DOI: 10.1530/endoabs.37.EP407

EP408

Microalbuminuria in children and adolescents with type 1 diabetes mellitus: predictive factors

Joana Nunes[1,2], Ricardo Monteiro[3], Daniela Amaral[4], Rosa Pina[4], Lurdes Lopes[4] & Catarina Limbert[4,5]
[1]Endocrinology, Diabetes and Metabolism Department, Centro Hospitalar São João, Porto, Portugal; [2]Faculty of Medicine, Porto University, Porto, Portugal; [3]Pediatrics Department, Centro Hospitalar Leiria Pombal, Leiria, Portugal; [4]Pediatric Endocrinology Department, Hospital D. Estefânia, Lisboa, Portugal; [5]Faculty of Medicine, Lisboa University, Lisboa, Portugal.

Objective
Microalbuminuria is usually the first microvascular complication of type 1 diabetes mellitus (T1DM). We aimed to identify its frequency, time of occurrence and related risk factors.
Methods
Clinical reports of 201 children followed in our institution were retrospectively analysed (diabetes duration 3.8 ± 3.6 years, age at diagnosis 8.1 ± 3.7 years, HbA1c value $9.0 \pm 1.7\%$). Statistical analysis was performed with SPSS version.21 for Windows. Results are expressed in frequencies and means $\pm$ S.D. Statistical significance was considered as P value < 0.05.
Results
Seventeen (ten females; seven males) patients (8.5%) presented microalbuminuria in a mean time of 5.5 ± 3.8 years: five children (29.4%) 2 years after diabetes onset and nine children (52.9%) 5 years after it (four children between 2 and 5 years of diabetes duration). In the logistic regression analysis, longer diabetes duration (6.3 ± 3.7 years vs 3.5 ± 3.5 years, $P = 0.005$, OR = 1.38), higher total cholesterol (TC) (180.6 ± 57.5 mg/dl vs 159.1 ± 31.0 mg/dl, $P = 0.03$, OR = 1.26), higher LDL (125.5 ± 36.3 mg/dl vs 110.9 ± 24.7 mg/dl, $P = 0.04$,

OR = 1.44), higher TG (133.3 ± 39.3 mg/dl vs 78.6 ± 38.4 mg/dl, $P = 0.006$, OR = 1.63), higher HbA1c (9.6 ± 1.9% vs 8.9 ± 1.7%, $P = 0.02$ OR = 1.88) and higher BMI (23.1 ± 4.9 kg/m^2 vs 20.3 ± 4.1 kg/m^2, $P = 0.02$, OR = 1.13) were associated with microalbuminuria. There were no statistical significant differences regarding gender, puberty and HDL-C.

Conclusions

In children, nephropathy can occur soon after T1DM onset. Besides poor metabolic control and longer diabetes duration, obesity and dyslipidemia seem to play a significant role. According to our results, we suggest yearly screening of microalbuminuria after T1DM onset and early treatment of dyslipidemia and obesity.

DOI: 10.1530/endoabs.37.EP408

EP409

Assessment of iodine status and thyroid structure changes in a cohort of patients with diabetes mellitus type 1 and comorbid chronic kidney disease in Belarus

Alena Sazonava[1], Tatiana Mokhort[1], Marina Astapovich[1] & Sergei Petrenko[2]
[1]Belarusian State Medical University, Minsk, Belarus; [2]International Sakharov Environmental University, Minsk, Belarus.

The aim was to assess iodine status and thyroid structure changes in a cohort of patients with diabetes mellitus type 1 (DM1) at different stages of comorbid chronic kidney disease (CKD) after achievement of adequate iodine status in Belarus. We examined 62 patients (20m; 42f; age 42.1 ± 12.07 years; BMI 26.14 ± 5.27 kg/m^2; duration of DM1 22.9 ± 8.67 years; age at DM1 onset 19.89 ± 12.72 years) at CKD stages 1, 2, 3, 5 ($n = 28$; 21; 12; 1 respectively). Urinary iodine excretion (UIE) in urine morning sample (UMS) was measured with the use of cerium–arsenite method approved WHO as a standard. Iodine deficiency (ID) is defined as a median urinary iodine concentration < 50 μ/l in a population. All data concerning ultrasound structure of thyroid gland (ThG) were determined as normal, reduced, increased volume (NVol, redVol, incrVol), homogeneity (hypo-, hyper-, homogeneous), local pathology (abs, single, multiple). In the examined group evaluating iodine supplementation in UMS lack of ID was registered – a median UIE at the time of survey was 115.5 mkg/l. Comparative analysis of patients in the subgroups according to CKD stages revealed reliable differences in level of UIE ($P = 0.0133$), total volume of ThG ($P = 0.0325$),and in homogeneity ($P = 0.040$).UIE in UMS correlates with urea plasma level ($r = -0.309$), GFR ($r = 0.420$), CKD stage ($r = -0.323$). Total volume of ThG correlates with plasma urea ($r = 0.313$) and creatinine levels ($r = 0.259$). Strong correlation was revealed between homogeneity and age at DM1 onset ($r = 0.292$). According to the ultrasound study of patients an incrVol was detected only in two patients (3.23%), in 33 revealed NVol (53.22%) and redVol in 27 patients (43.55%). Structural changes in ThG such as hypoechoic structure were reported in 24 patients (38.71%). Single and multiple pathology was recorded in 16 and seven patients respectively (25.81 and 11.29%). ID was not registered in examined population of patients that demonstrates the effectiveness of iodine prophylaxis. Revealed a direct correlation between level of UIE and CKD stage can lead to a variety of structural changes in ThG which requires close monitoring of patients with reduced renal function.

DOI: 10.1530/endoabs.37.EP409

EP410

Association of dyslipidaemia, chronic kidney disease and hypertension with carotid atherosclerosis in patients with type 2 diabetes mellitus

Volha Vasilkova[1], Tatiana Mokhort[2], Elena Naumenko[3] & Natalia Filipcova[3]
[1]Gomel State Medical University, Gomel, Belarus; [2]Belarusian State Medical University, Minsk, Belarus; [3]The Republican Research Centre for Radiation Medicine and Human Ecology, Gomel, Belarus.

Introduction

Atherosclerotic complications are the leading causes of morbidity and mortality among patients with DT2.

Aim

To investigate the possible role of dyslipidaemia, hypertension and chronic kidney disease (CKD) on the characteristics of carotid atherosclerosis (presence of plaque, carotid IMT and total plaque area) in patients with DT2.

Material and methods

Patients aged 60–75 years with DT2 were included in this study. Control group included 24 healthy subjects the same age. Other atherosclerosis risk factors of subjects, including smoking, hypertension, dyslipidaemia, and CKD, were identified with a questionnaire and a blood test. The IMT was measured using automated edge detection software as the distance between the lumen–intima interface and the media–adventitia interface. Atherosclerotic plaque was defined as a focal structure encroaching into the arterial lumen of 0.5 mm or 50% of the surrounding IMT value or IMT of > 1.5 mm. Total plaque area (TPA) was calculated as the sum of all plaque areas.

Results

We divided all patients (DT2 and control) into three groups: Group 1 ($n = 24$) – patients did not have any additional atherosclerosis risk factor, Group 2 ($n = 25$) – patients had one additional atherosclerosis risk factor, and Group 3 ($n = 43$) – patients had two or three additional atherosclerosis risk factors. Using multiple linear regression analysis adjusted for confounding factors, IMT and TPA were significantly correlated with age > 60 years ($\beta = 0.359$, $P < 0.0001$; $\beta = 0.263$, $P < 0.0001$), hypertension ($\beta = 0.041$, $P = 0.003$; $\beta = 0.126$, $P < 0.0001$), dyslipidemia ($\beta = 0.066$, $P = 0.0001$; $\beta = 0.125$, $P < 0.0001$) and CKD ($\beta = 0.054$, $P = 0.003$; $\beta = 0.165$, $P < 0.0001$), respectively. However, gender (men) was not significantly correlated with IMT ($P = 0.171$) and TPA ($P = 0.112$).

Conclusion

The presence of dyslipidaemia, hypertension, and different CKD status were predictors of carotid plaque.

DOI: 10.1530/endoabs.37.EP410

EP411

Validation of self-reported oral health measures for predicting periodontitis among adult Filipinos with type 2 diabetes mellitus

Tom Edward Lo, Ma. Cristina Lagaya-Estrada, Cecilia Jimeno & Gabriel Jasul
Philippine General Hospital, Manila, The Philippines.

Diabetes mellitus is currently being recognised as a global health problem. The likelihood of periodontal disease among diabetics is thrice and progresses rapidly when uncontrolled. Diabetics were less likely to see a dentist than to seek consult with a doctor for diabetes care. A cheap and easy way of clinical assessment via self-reported oral health questionnaire would be of great use especially in a developing country like The Philippines. This study aims to validate self-reported oral health measures, socio-demographic and medical variables in predicting the severity of periodontitis in Filipino adults with type 2 diabetes. The validated self-reported oral health questionnaires created by the CDC Periodontal Disease Surveillance Project was translated into Filipino and used. A cross-sectional study of 180 participants was conducted in a single institution. Multivariable logistic regression analyses was used to determine significant predictors of serious periodontitis. Socio-demographic and medical variables considered to be significantly predictive of serious periodontits were male sex (OR = 2.17), low educational status (OR = 2.98), poor glycaemic control (OR = 2.58), less frequent dental visits (OR = 2.77) and teeth loss > 6 (OR = 5.02). Self reported oral health variables shown to be significantly predictive of serious periodontitis included gum disease – Q1 (OR = 8.33), state of gum health – Q2 (OR = 0.39), loose teeth – Q3 (OR = 63.0), brushing of teeth – Q4 (OR = 0.65), use of mouthwash – Q4 (OR = 0.69) and poor tooth appearance – Q5 (OR = 48.42). A recommended set of questions and proposed scoring system based on the logistic regression analysis of each predictors' strength was then formulated. The use self-reported oral health questions appears to be a potentially useful screening tool for predicting the presence of serious periodontitis among type 2 diabetics locally where resources are limited and routine clinical oral examinations are not feasible. This will provide a cost-effective and rapid method of identifying patients who are in need of immediate dental evaluation and would benefit most to a dental referral.

DOI: 10.1530/endoabs.37.EP411

EP412

The effect of MCP-1 A-2518G polymorphism on development of diabetic coronary artery disease

Gokhan Bagci[1,2], Binnur Bagci[1] & Bedia Cakmakoglu[2]
[1]Cumhuriyet University, Sivas, Turkey; [2]Istanbul University, Istanbul, Turkey.

Introduction
Inflammatory markers play an important role in the development of type 2 diabetes and coronary artery disease. Monocyte chemoattractant protein-1 (MCP-1) is a member of the C-C chemokine family and a potent chemotactic factor for monocytes.

The aim of our study was to investigate the effect of MCP-1 A-2518G polymorphisms on the development of diabetic coronary heart disease.

Subjects and methods
53 diabetic patients with coronary heart disease, 64 diabetic patients without coronary heart disease and 61 healthy controls were genotyped. Diabetes was diagnosed according to the criteria of the American Diabetes Association (ADA) and the non-diabetic subjects were selected according to no past history of diabetes mellitus or impaired glucose tolerance. PCR–RFLP method was used for genotyping.

Results
There were significant differences between diabetic patient with coronary heart disease and control groups in MCP-1 A-2518G genotype (P: 0.01%2 χ^2: 9.11) and allele distribution (P: 0.01%2 χ^2: 6.53). MCP-1 AA genotype was significantly increased in coronary artery patients compared with controls but MCP-1 G allele frequency was increased in controls.

Conclusion
We found that MCP-1 2518 AA genotype may associate with diabetic coronary artery disease susceptibility while G allele seems to be have protective effect against diabetic coronary disease.

Disclosure
The present work was supported by the Research Fund of Istanbul University Project No. 2874.

DOI: 10.1530/endoabs.37.EP412

EP413

Phenotype-directed personalisation of therapy in type 2 diabetes mellitus patients and criteria of prescription

Tatjana Mikijanska, Viktors Snigirovs & Valdis Pirags
University of Latvia, Riga, Latvia.

Methods
We studied 228 patients with T2DM treated in Pauls Stradins Clinical University Hospital in Endocrinology Department from Jan 2013 to Sep 2014. The greatest attention was paid to the patients' biochemical analyses, such as triglycerides (TG), c-peptide, HbA1c and prescribed treatment, as well as BMI and the doctor who treated each patient. Phenotypically patients were divided into four major groups. The first group included 73 patients with chronic kidney disease (GFR <60 ml/min per 1.73 m^2), the second – 31 patient with obesity (BMI >30 kg/m^2), 66 persons represented older patients group (>65 years old) and 58 – with early diabetes (<10 years).

Results
For patients with obesity, treatment was started with insulin and metformin combination; chronic kidney disease group – with insulin monotherapy; in groups of old patients (>65 years) and early diabetes patients – with insulin monotherapy. Insulin monotherapy was used for patients with c-peptide 0.1–0.9 ng/l; for patients with c-peptide 1–2 ng/ml was used metformin combination with insulin, but patients with c-peptide more than 2 ng/ml were treated more often with DPP-4/metformin combination with insulin. There was no correlation between HbA1c level and prescribed therapy. For patients with TG level from 1.7 to 5.6 mmol/l was used metformin together with insulin, with TG <1.7 mmol/l – only insulin, but with TG over 5.7 mmol/l DPP-4/metformin combination with insulin. We found some correlation between prescribed therapy and treating physicians: three of five physicians treated their patients more often with insulin. One treated patients mostly with combination of insulin and metformin, while last – with combination of DPP-4/metformin and insulin.

Conclusion
As T2DM is a special medical condition that requires an individualised approach to each patient to achieve adequate glycaemia and HbA1c levels.

DOI: 10.1530/endoabs.37.EP413

EP414

Glucogenic hepatopathy: a rare and underdiagnosed condition in type 1 diabetes

Demet Ozgil Yetkin
Kolan International Hospital, Istanbul, Turkey.

Introduction
Glycogenic hepatopathy (GH) has been reported as a very rare and under recognized complication in longstanding poorly controlled type 1 diabetes patients. GH is characterised by transient elevation of liver transaminase and hepatomegaly caused by reversible and excessive glycogen accumulation in hepatocytes. Here we report a 20 years old type 1 poorly controlled diabetic female patient with elevated transaminases.

Clinical presentation
A 20-year-old type 1 diabetic female with poor glycaemic control, complicated by recurrent diabetic ketoacidosis (DKA) was admitted, with symptoms of fatigue, nausea, abdominal pain, and vomiting. Her glycaemia had been poorly controlled with several episodes of DKA for several years. Her physical examination revealed hepatomegaly. Abdominal US showed mild fatty change of liver and mild hepatomegaly. Her HbA1c, 14.2%, SGOT: 79 (0–35) U/l, SGPT: 97 (0–35) U/l, ALP: 125 (47–119) U/l, and GGT: 247 (4–24) U/l. Auto-antibody including anti-nuclear antibody (ANA), smooth muscle antibodies (ASMA), and mitochondrial antibodies (AMA) were all negative. Thyroid function test, serum cupper, alfa1 antitripsin, and serum ceruloplasmin were also normal. The serologic findings for viral infection such as IgM anti-HAV, HBsAg, anti-HCV, HCV-RNA, cytomegalovirus, and Epstein–Barr virus were also all negative. Serum albumin and coagulation tests remained normal. She was not an alcohol or drug consumer and was not taking any medication except insulin. In addition, she did not show any symptom and sign compatible with acute hepatitis. So, we recommend her for a liver biopsy to elucidate the cause of acute elevation of liver enzyme. In hematoxylin and eosin stain, liver biopsy showed normal liver architecture, however, the hepatocytes were diffusely swollen with pale cytoplasm. The periodic acid-Schiff (PAS) staining showed abundant glycogen accumulation within hepatocytes. So, histologically, it was diagnosed as a glycogenic hepatopathy. Six weeks later, her transaminases were drooped to high normal levels via glycaemic control.

Conclusion
GH is a rare cause of increased transaminases in diabetic patients. Clinician awareness of GH should prevent diagnostic delay and will provide better insight into the prevalence of GH.

DOI: 10.1530/endoabs.37.EP414

EP415

Assessment of dependence of the hypoglycaemic episodes frequency on gender factor

Elena Mahlina[1], Yana Navmenova[2] & Tatiana Mokhort[3]
[1]Republican Research Centre for Radiation Medicine and Human Ecology, Gomel, Belarus; [2]Gomel State Medical University, Gomel, Belarus; [3]Belarusian State Medical University, Minsk, Belarus.

Objective
Assessment of the frequency of hypoglycaemic episodes during daily monitoring of glucose in the subcutaneous water of women and men with type 1 diabetes mellitus.

Methods
The study of daily dynamics of glucose has been performed with continuous glucose monitoring system (CGMS) Medtronik MINIMED company (USA). The study involved 162 patients with type 1 diabetes mellitus. The patients were divided into two groups: group 1 – women with regular menstrual cycle ($n=117$) and group 2 – men ($n=45$). The groups were compared in mean age (29.14 ± 7.56 years) and duration of type 1 diabetes mellitus (10.74 ± 7.67 years).

Results
In the first group of women 53%, registered hidden hypoglycaemic episodes, and 47% were not observed ($P<0.05$). In the second group of men 69% has been registered hidden hypoglycaemic episodes, and 31% were not observed ($P<0.01$). As for the incidence of hidden hypoglycaemic episodes between the groups, the significant differences were not observed (in the first group – 53% and in the second group – 69%), $P>0.05$. Depending on the time of day, the incidence of hidden hypoglycaemic episodes (in the first group – 83% and in the second group – 75%) prevailed in comparison with explicit (in the first group – 17% and in the second group – 25%), $P<0.001$. The daytime incidence of hypoglycaemic episodes in the first group was 72%, in the second group was 85% in comparison with the incidence of night hypoglycaemic episodes (in the first group – 28% and in the second group – 15%), $P<0.05$.

Conclusions
i) Regardless of gender, the bulk of the cases occurred in hidden hypoglycaemic episodes compared with explicit ones. ii) The incidence of hidden day-time hypoglycaemic episodes was prevailed over the night incidence of hypoglycaemic episodes, regardless of gender. iii) The incidence of hidden hypoglycaemic episodes does not depend on gender.

DOI: 10.1530/endoabs.37.EP415

EP416

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

Murat Karakulak[1], Ugur Saygili[2], Muzaffer Temur[3], Özgür Yilmaz[3], Elif Pelin Özün Özbay[4], Mehmet Calan[5] & Hese Cosar[6]
[1]Department of Obstetrics and Gynecology, Silivri State Hospital, Istanbul, Turkey; [2]Department of Obstetrics and Gynecology, Dokuzeylul University Medical School, Izmir, Turkey; [3]Department of Obstetrics and Gynecology, Manisa Merkezefendi Hospital, Manisa, Turkey; [4]Department of Obstetrics and Gynecology, Aydin Obstetrics and Pediatrics Hospital, Aydin, Turkey; [5]Department of Endocrinology, Izmir Bozyaka Research Hospital, Izmir, Turkey; [6]Division of Neonatology, Department of Pediatrics, Manisa Merkezefendi Hospital, Manisa, Turkey.

Purpose
The purpose of this study was to analyse ghrelin concentrations in the umbilical cord of pregnant women with a diagnosis of gestational diabetes mellitus. The relationship between ghrelin concentrations and birth weights was investigated.
Materials and methods
Sixty pregnant women with gestational diabetes mellitus and 64 healthy pregnant women with three oral glucose tolerance test results within normal limits were included in the study. Following birth but before extraction of the placenta, 10-ml blood samples were drawn from the umbilical vein in both groups. Ghrelin concentrations were measured.
Results
The mean birth weights of the babies born to mothers with GDM were higher than those in the control group ($P=0.04$). The cord blood ghrelin levels in pregnant women with GDM were significantly lower than those of the healthy women in the control group (879.6 pg/ml vs 972.2 pg/ml; $P=0.03$). The umbilical cord blood ghrelin concentrations in pregnant women with GDM undergoing insulin therapy were significantly lower than those of the control group (792.61 pg/dl vs 972.2 pg/dl; $P=0.01$). Inverse correlations were detected between umbilical cord blood ghrelin levels and birth weights of the babies both in the group with GDM patients ($r: -0.785$; $P=0.001$) and in the control group ($r: -0.749$; $P=0.001$).
Conclusions
In pregnant women with GDM, umbilical cord ghrelin concentrations are closely related to the birth weights of the babies. Ghrelin presumably may be among the factors influencing foetal development potentially with its GH stimulating effects or by means of other mechanisms.

DOI: 10.1530/endoabs.37.EP416

EP417

The relationship between metabolic syndrome and albuminuria in patients with type 2 diabetes mellitus

Osman Sahin, Serap Baydur Sahin, Teslime Ayaz & Ekrem Algun
Recep Tayyip Erdogan University Medical School, Rize, Turkey.

Background and aims
Obesity, as a central piece inside metabolic syndrome, is as an independent risk factor for the onset, aggravated course, and poor outcomes of chronic kidney disease (CKD) including diabetic nephropathy (DN). Our aim was to investigate the relationship between metabolic syndrome (MS), diabetic nephropathy and renal function in patients with type 2 diabetes mellitus (T2DM).
Materials and Methods
197 patients with T2DM (mean age; 56.1 ± 10.2 years, female/male; 127/70) were enrolled. NCEP ATP III criteria was used for the diagnosis of MetS. Albuminuria and estimated glomerular filtration rate (eGFR) were measured.
Results
79.3% of the patients had MS. HbA1c levels were similar in patients with (8.5 ± 2.2 vs 8.5 ± 2.1) and without MS ($P=0.888$). The frequencies of diabetic retinopathy and neuropathy were not different in patients according to the presence of MS ($P>0.05$). Prevalence of microalbuminuria (32.2% vs 46%) and macroalbuminuria (12.3% vs 7.7%) was similar in subjects with and without MS ($P=0.248$). We did not find a decrease in eGFR in patients with MS compared to the patients without MS. While uric acid levels were higher in patients with MS (5.5 ± 1.5 mg/dl vs 4.7 ± 1.5 mg/dl, $P=0.006$), hsCRP values did not differ ($P=0.689$). 72.4% of the subjects were obese and the prevalence of albuminuria was not different in obese and nonobese patients ($P=0.596$).
Conclusion
In this study we did not find an association between obesity, MS, and DN.

DOI: 10.1530/endoabs.37.EP417

EP418

Achievement of recommended glucose, lipid, and blood pressure targets in patients with type 2 diabetes mellitus

Ines Barka, Ines Slim, Senda Ouerdeni, Koussay Ach, Amel Maaroufi, Yosra Hasni, Maha Kacem, Molka Chaieb & Larbi Chaieb
Department of Endocrinology, Farhat Hached University Hospital, Sousse, Tunisia.

Background
Patients with type 2 diabetes mellitus (T2DM) have a greater risk for cardiovascular morbidity and mortality than those without T2DM. This risk is even further aggravated if they also suffer from hypertension and/or dyslipidaemia. However, better cardiovascular outcome can be reached by tight control of blood glucose, serum lipids, and blood pressure (BP).
Patients and methods
One hundred and nineteen patients were consecutively enrolled. Well-controlled metabolic parameters are defined as follows: HbA1c $<7.0\%$, BP $<140/90$, and LDL cholesterol (LDL-c) <2.6 mmol/l. For all patients, anthropometric measurements and metabolic risk factors were carried.
Results
A total of 119 subjects (61 men and 58 women) were included. The mean age was 58.0 ± 10.6 years old. Of these patients, 60% had hypertension. The mean value of HbA1c was $8.8\pm2.3\%$ and glycaemic control was optimal (HBA1c $<7\%$) in $20.0\pm4.1\%$. Mean values of systolic BP and diastolic BP were 135 ± 16 and 76 ± 12 mmHg respectively. BP therapeutic goal was achieved in $50\pm5\%$ of patients. The mean value of LDL-c was 2.7 ± 1 mmol/l. We noticed that 48.3% of patients had LDL-c <2.6 mmo/l. All three targets were achieved only by 5% of patients ($n=6$).
Conclusion
Even if targets of assessed metabolic parameters are known to be important to achieve in diabetic patients in order to reduce cardiovascular risk, our results shows that few individuals had achieved goals; especially oh HbA1c compared to lipids and BP goals. An urgent action is needed to increase the proportion of these individuals achieving recommended glycaemic goals by adapting lifestyle measures and medications and also by using motivational interviewing to insure therapeutic adherence.

DOI: 10.1530/endoabs.37.EP418

EP419

***Staphylococcus aureus* nasal carriage and related risk factors in diabetic foot patients**

İlhan Kurultak[1], Mustafa Altay[2], Salih Cesur[3], Eda Yıldız[4] & Murat Duranay[5]
[1]Department of Nephrology, Medical Faculty, Trakya University, Edirne, Turkey; [2]Department of Endocrinology and Metabolism, Keçiören Education and Research Hospital, Ankara, Turkey; [3]Department of Infectious Disease and Clinical Microbiology, Ankara Education and Research Hospital, Ankara, Turkey; [4]Department of Microbiology, Ankara Education and Research Hospital, Ankara, Turkey; [5]Department of Nephrology, Ankara Education and Research Hospital, Ankara, Turkey.

Introduction
Infections are the major cause of increased mortality and morbidity rate in diabetic foot patients. There are little data in literature about the effects of *Staphylococcus aureus* nasal carriage on DF infection, the risk factors that

influence nasal carriage and its incidence in diabetics. We aimed to detect of the incidence, risk factors and relationship between wound culture and *S. aureus* nasal carriage in diabetic patients who have DF with this study.
Material and methods
The study was designed as a prospective, cross-sectional, controlled study. Group 1 ($n=40$): nondiabetic patients, group 2 ($n=40$): diabetics patients without DF, and group 3 ($n=40$): diabetics patients with DF. The incidence of *S. aureus* nasal carriage and effects of determined factors to nasal carriage were investigated in these three groups. The relationship between nasal carriage and wound culture was analysed in the last group.
Results
We found the incidence of *S. aureus* nasal carriage 17.5, 20, and 10% in the groups 1–3 respectively ($P=0.47$). Determined parameters (age, sex, usage of insulin/oral anti-diabetic drugs, time of diabetes, level of HbA1c, and levels of fasting and after meal glucose) did not affect the *S. aureus* nasal carriage. We did not detect the relationship between wound cultures and nasal swap cultures in group 3. We observed no effect of the history of antibiotic usage in the last 6 months and existence of hospitalization or operation on *S. aureus* nasal carriage.
Conclusion
We detected that having diabetes and/or DF did not alter the risk of *S. aureus* nasal carriage and also carriage did not affect the results of wound culture. Better designed studies are needed for the detection of possible relationship between the factors belongs to the patients who have higher risk for *S. aureus* infections and nasal carriage.

DOI: 10.1530/endoabs.37.EP419

EP420

The role of fetuin A as a biomarker of atherosclerosis and its relation to type 2 diabetes

Nermeen Sheriba, Rania Sayed, Merhan Nasr, Sara Shelbaya & Magdy Abbas
Ain Shams University, Cairo, Egypt.

Background
Hyperglycaemia produces various changes in the vascular tissue at the cellular level that accelerates the atherosclerosis. There is a direct correlation among carotid arterial stiffness and serum fetuin-A level. Fetuin-A is a marker of the inflammatory nutritional state and acts as a protective agent because it solubilises the calcium phosphate salt.
Aim of this work
To study the role of fetuin A in atherosclerosis and its association with type 2 diabetes.
Subjects and methods
This cross sectional study was conducted on 50 subjects aged from 40 to 60 years old divided into group I: 20 T2DM patients having atherosclerosis. Group II: 20 non diabetic patients having atherosclerosis. Group III: ten healthy subjects as control group. They were subjected to full clinical history, thorough clinical examination, laboratory investigations including fasting and 2-h postprandial blood glucose level, HbA1c, lipid profile, measurement of plasma fetuin-A level using ELISA, and measurement of carotid intimal thickness using duplex ultrasound.
Results
There was a highly significant difference between the three groups as regard SBP, DBP, FBG, PBG, HbA1c, TG, HDL-c, LDL-c, carotid intimal thickness, and fetuin-A level ($P<0.001$) and on comparing the diabetics with atherosclerosis (group I) with non diabetics with atherosclerosis (group II) we found a highly statistical significant decrease in plasma fetuin-A level ($P<0.001$) being lower in group (I) and a highly significant increase in carotid intimal thickness, SBP, and LDL-c ($P<0.001$) in group I. We also found a highly significant negative correlation between fetuin-A and SBP, LDL-c, and carotid intimal thickness ($P<0.001$). A significant positive correlation was also found between carotid intimal thickness and SBP, HbA1c, and LDL-c ($P<0.05$). We found that the cutoff point of fetuin-A level using the ROC curve is 125 µg/ml with 100% sensitivity, 90% specificity, 97.1% accuracy, and a positive predictive value of 97.6%.
Conclusion
Our results postulate that there is an association between lower plasma fetuin-A level and the development of atherosclerosis especially in those having type 2 diabetes.

DOI: 10.1530/endoabs.37.EP420

EP421

Association of plasma fetuin-A levels and peripheral vascular disease in type 2 diabetic patients

Salah Shelbaya, Rania Sayed, Merhan Nasr & Ahmed Abd El Aziz
Ain Shams University, Cairo, Egypt.

Background
Diabetes is a risk factor for both PAD and PAD-associated mortality. Diabetic patients have worse arterial disease and a poorer outcome than nondiabetic patients. Fetuins are blood proteins made in the liver more abundant in fetal blood. Fetuin-A is regarded as an inhibitor of systemic calcification.
Aim of this work
To assess the relationship between plasma fetuin-A levels and peripheral vascular disease in type 2 diabetes mellitus.
Subjects and methods
This cross sectional study was conducted on 50 subjects aged from 50 to 65 years old divided into group 1: 20 T2DM patients with PVD. Group 2: 20 T2DM patients without PVD. Group 3: ten healthy subjects as control group. They were subjected to full clinical history, thorough clinical examination, laboratory investigations including fasting and 2-h postprandial blood glucose level, HbA1c, measurement of plasma fetuin-A level using ELISA and arterial Doppler ultrasound on peripheral vasculature for assessment of ankle peak systolic velocity (APSV).
Results
There was a highly significant increase in weight and BMI, FBG, and PBG in group 1 (diabetics with PVD) and group 2 (diabetics without PVD) than group 3 (control) ($P<0.001$). While there was a highly significant decrease in plasma fetuin-A level and APSV in diabetics with PVD when compared with diabetics without PVD and also when compared with control ($P<0.001$) While there was no statistical significant difference between group 2 (diabetics without PVD) and group 3 (control) as regard fetuin-A level ($P=0.065$). There was a highly statistical significant decrease in plasma fetuin-A level and APSV ($P<0.001$) being lower in group 1 than group 2 but there was no statistical significant difference as regard weight, height, BMI, FBG, PBG, and HbA1c. There was a highly significant positive correlation between fetuin-A and APSV ($r=0.737$, $P<0.001$) but a negative non-significant correlation between fetuin-A and the other parameters.
Conclusion
These results postulate an association between lower plasma fetuin-A level and peripheral vascular disease in type 2 diabetic patients.

DOI: 10.1530/endoabs.37.EP421

EP422

Glycaemic variability in pregnant women with gestational diabetes

Nida Oztop, Selda Celik, Yildiz Tutuncu, Elif Bagdemir, Cemile Idiz, Ayse Kubat Uzum, Ilhan Satman & Nevin Dinccag
Endocrinology and Metabolism Division, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey.

Introduction
The accurate and comprehensive assessment of glycaemic control in pregnant with gestational diabetes (GDM) is important for preventing foetal complications. We aimed to determine glycaemic variation on women with GDM with using a continuous glucose monitoring system (CGMS) and to investigate the relationship between reflecting glucose markers such as HbA1c, fructosamine (FRM), and 1,5-anhydroglucitol (1,5-AG).
Materials and methods
31 women with GDM on diet therapy only (mean age 31.9 ± 6.9 years, gestational week ≥35) were recruited from outpatient clinic. Those patients were screened by self-monitoring blood glucose (SMBG) and monitored for three consecutive days to obtain mean daily glucose data; glycaemic fluctuations were evaluated using postprandial incremental area under curve (AUC) and percent of mean absolute difference (MAD%). Venous blood samples were collected to measure HbA1c, FRM, and 1,5-AG.
Results
Prepregnancy BMI of participants was 26.2 ± 5.9 kg/m^2, weight gain during pregnancy was obtained as 12.2 ± 3.5 kg; levels of reflecting glucose markers were measured as following: HbA1c 5.0 ± 0.3 %, FRM 2.1 ± 0.2 µmol/l, and 1,5-AG 17.0 ± 4.9 ng/ml; according the results of CGM, MAD % was found as 6.7 ± 3.1%, the total number of fluctuations in glucose levels were counted as 5.8 ± 3.6. Glucose figures, measured by SMBG or CGMS were found similar (82.9 ± 10.2 and 86.1 ± 10.3 mg/dl); I statistically, there wasn't any correlation between

determinants of CGM and other glucose reflection parameters. It was realised that birth of weight and size of head circumference of babies were affected by maternal glucose levels.
Conclusion
Although, it seems that normoglycaemia is sustained, there should be glucose variability in diabetic patients especially during pregnancy and all known glucose reflecting parameters do not show fluctuations. CGMS is an alternative method for detecting glucose variations in spite of having difficulties to afford and apply the tool. We concluded that higher glucose fluctuations were observed on pregnants with GDM who have high triglyceride at fasting and high glucose levels at third hour of OGTT at the beginning.
Disclosure
This research was supported by research fund of Istanbul University. Grant number: 44800.
DOI: 10.1530/endoabs.37.EP422

EP423

Sexual function in women with diabetes at a Diabetes Care Unit

Eva-Karin Brannestam
Höglandssjukhuset, Eksjö, Sweden.

The true prevalence of sexual dysfunction in women with diabetes is difficult to estimate. Studies of the area have shown varying and conflicting results. There is also disagreement about the conditions that influence this relationship and the risk factors that can be linked to the phenomenon. The purpose of this study was to investigate sexual function in women with diabetes at a Diabetes Care Unit. The study was conducted using a quantitative approach. Fifty women aged 18–65 years with type 1 or type 2 diabetes were enrolled in the study in which respondents were asked to complete a questionnaire containing background questions and the questionnaire, Female Sexual Function Index (FSFI). Twenty-nine women with diabetes (60%) showed a total score below 30, which can be classified as sexual dysfunction. Those domains that showed the lowest scores of these 29 women were the domains desire, orgasm and satisfaction. Sixty-four percent of the 50 women had not received any information about sexuality linked to diabetes, but 82% thought that it was quite important or very important to discuss any changes in sexuality. The prevalence of sexual dysfunction in women with diabetes is a phenomenon that one cannot disregard. A deeper knowledge in this area would be desirable. This study demonstrated that there might be women with diabetes who experience sexual dysfunction. The majority of the women felt that it was important to discuss changes in sexuality linked to diabetes. In addition, the majority stated that it was not informed about the area through their clinic.

DOI: 10.1530/endoabs.37.EP423

EP424

Particular characteristics of breath during night sleep in type 1 diabetes patients

Ina Darashkevich[1], Tatsiana Mokhort[2], Lola Nikonova[1], Serhej Tishkovsky[1] & Elina Davydchik[1]
[1]Grodno State Medical University, Grodno, Belarus; [2]Belorussian State Medical University, Minsk, Belarus.

Objective
Assessing the impact of glycaemic control on indicators of breathing during night sleep in type 1 diabetes patients.
Methods
Continuous blood glucose monitoring by 'SGMSGold' (Medtronik MINIMED) with estimation of average glycaemic value (AG) and other parameters; polysomnographic monitoring by 'SOMNOlab 2 (PSG) Polysomnography (R&K)'. Group 1 included patients with AG levels <8.0. Group 2: AG $>$ 8.0 mmol/l regardless of HbA1c (7.50 (5.00–9.40) and 8.01 (5.60–12.00)% respectively).
Results of the study
The differences in the characteristics of sleep and periods of hyperglycaemia, normoglycaemia, AG, MGL in the comparison groups were detected. There was an inverse relationship between AG <8.0 mmol/l and the mean respiratory rate TST, deep sleep S4 stage ($r=-0.64$), sleep latency ($r=-0.58$); direct correlation between amount of apnoea ($r=0.74$ and $r=0.90$); MGL with the duration of slow wave sleep ($r=-0.61$) and reverse with RE NREM ($r=0.57$).

Indicator	Group 1, mean (min–max)	Group 2, mean (min–max)
Amount (*n*)	13	20
Age	34.5 (25.0–54.0)	35.9 (20.0–56.0)
The average value of blood glucose (AG) (mmol/l)	6.6 (3.2–8.0)*	10.0 (8.1–16.6)
Hyperglycaemia (%)	11.5 (0.0–22.0)*	43.5 (10.0–86.0)
Hypoglycaemia (%)	14.4 (0.0–80.0)*	3.75 (0.0–25.0)
Normoglycaemia (%)	74.1 (20.0–92.0)*	52.7 (0.0–77.0)
The minimum glucose level during sleep (MGL) (mmol/l)	3.7 (2.0–6.1)*	5.8 (2.5–11.5)
The index of apnoea/ hypopnea (AI)	0.4 (0.3–14.8)*	2.1 (0.0–16.4)
The average duration of all respiratory events (RE) during total sleep time (TST)	25.0 (0.0–41.0)*	15.8 (0.00–40.0)

*$P<0.05$.

Conclusions
AG <8 mmol/l is associated with violations of the respiratory rate and sleep latency. It is noted that the MGL correlated with the duration of SWS, indicating that the effect of hypoglycaemia on sleep quality, the average length of all RE during TST.

DOI: 10.1530/endoabs.37.EP424

EP425

Obstructive sleep apnoea, incident type 2 diabetes mellitus, and cardiovascular risk

N Muñoz-Rivas, M Mendez-Bailon, M J Buendia, F J del Cañizo-Gomez, A Partido, A Alcorta, J de Miguel-Llanes & F J Solis-Villa
Hospital Universitario Infanta Leonor, Madrid, Spain.

Obstructive sleep apnoea (OSA) is a condition strongly associated with cardiovascular disease. Obesity is often related to both clinical problems and it is also a risk factor for incident type 2 diabetes mellitus (T2DM).
Aim
To assess cardiovascular risk among a cohort of patients with OSA in order to identify and optimise treatment of high risk patients.
Methods
Prospective study that included 72 patients with OSA under continuous positive airway pressure treatment. In all patients hypertension, T2DM, dyslipidaemia, smoking status, and history of cardiovascular disease were assessed; blood pressure (BP), body weight and height, waist circumference and neck size were measured; and BMI was calculated. Blood and urine samples were taken to evaluate fasting plasma glucose, cholesterol levels, glomerular filtration rate, microalbuminuria and HbA1c. T2DM was diagnosed with ADA criteria, and score was used to evaluate global cardiovascular risk and stratify high risk patients (score ≥ 5) in non diabetics.
Results
Of the 72 patients, 73% were male. Mean age was 52 years, and mean BMI 34.4 kg/m^2. At baseline, 52% had hypertension, 40% uncontrolled systolic BP, 50.8% dyslipidemia, 15% T2DM, 39% impaired fasting glucose (IFG), 7.6% previously unknown DM, 8.9% microalbuminuria, 44% a score >5%, and 38% were current smokers. There was a significant relationship between neck size (43.50 cm vs 40.52 cm, $P<0.05$) and BMI (35.7 kg/m^2 vs 33.4 kg/m^2, $P<0.05$) with IFG, and a significant association between apnoea–hypopnoea index (48.8 vs 37.3 apnoea/h, $P<0.05$) with high cardiovascular risk.
Conclusions
Compared with the general population, patients with OSA studied had a high cardiovascular risk and a high frequency of IFG and T2DM, especially in those with grade 2 obesity and a bigger neck size. Screening for diabetes and other cardiovascular risk factors in this population may be of particular interest.

DOI: 10.1530/endoabs.37.EP425

EP426

Simultaneous pancreas–kidney transplantation effect on stabilisation/progression of diabetic complications in patients with type 1 diabetes

Alexandra Glazunova[1], Margarita Arutyunova[1], Gulia Musaeva[5], Minara Shamkhalova[1], Marina Shestakova[1,5], Yan Moysyuk[2], Alexey Pinchuk[3], Ilya Dmitriev[3] & Sergey Arzumanov[4]
[1]Research Centre of Endocrinology, Moscow, Russia; [2]Academician V.I. Shumakov Federal Research Centre of Transplantology and Artificial organs, Moscow, Russia; [3]N.V. Sklifosofskiy Moscow Health Department, Research Institute of Emergency Care, Moscow, Russia; [4]Federal Research Centre of Urology, Moscow, Russia; [5]I.M. Sechenov First Moscow State Medical University, Moscow, Russia.

Objective
To evaluate the simultaneous pancreas–kidney transplantation (SPK) effect on stabilisation/progression of complications in patients with T1DM.
Materials and methods
The study included 16 patients after SPK. Eleven peoples received standard triple immunosuppressive therapy during the study period, five patients canceled steroid therapy after 6 months. The average age was 34 years old (31; 40), duration of T1DM 22 years (20.5; 28), the duration of diabetic nephropathy10 years (8; 14.5). The duration of dialysis therapy was 2 years (0.9; 2.5). All patients remained in the study for at least months 21 (10; 36) after the transplantation. Pancreas transplant chronic rejection with normal kidney transplant function was observed in one patient in 1 year after the operation.
Results
The mean level of HbA1c before the study was 8.65% (8.4; 9.1), then decreased to 5.6% (5.5; 5.8) after SPK. According to a continuous glucose monitoring system using «iPRO2» euglycaemia (glycaemia (mmol/l) 3.9–8.9–89%, lower than 3.9–11%, and higher than 8.9–0%) was marked during the day. The level of C-peptide was 2.02 ng/ml (1.07; 2.77), of insulin 12.5 mkE/ml (11.4; 15.3), and GFR 76 ml/min per 1.73 m^2 (68; 90). All patients had normoalbuminuria, normal levels of hemoglobin 120 g/l (112; 130), parathormone 77.3 pg/ml (60.4; 92.5), phosphorus 1.2 mmol/l (1.05; 1.4), and blood pressure 110 mmHg (100.0; 120). The proliferative diabetic retinopathy progression which required vitrectomy and additional laser panretinal photocoagulation sessions was observed in 18.75% of patients. Nonstenotic atherosclerosis of the lower extremities was detected in 13 peoples, ulcerative defects in the lower limbs in five patients and chronic osteoarthropathy progression in four cases.
Conclusions
Despite the euglycaemia and renal function normalisation after SPK the progression of diabetic complications was observed. This fact indicates the need of further monitoring and treatment in this category of patients.

DOI: 10.1530/endoabs.37.EP426

EP427

Influence of diabetic polyneuropathy on the severity of pain in patients with osteoarthritis of the knee joints and type 2 diabetes mellitus

Leonid Strongin, Ksenia Korneva & Elena Trifonova
Nizhny Novgorod State Medical Academy, Nizhny Novgorod, Russia.

Introduction
Osteoarthritis (OA) and type 2 diabetes mellitus (T2DM) are common diseases among middle-aged and elderly persons. Aim of our study was to assess the influence of diabetic polyneuropathy (DPN) on the severity of pain in OA in patients with concomitant T2DM.
Methods
80 female patients with OA of the knee joints in combination with T2DM were examined. The severity of gonarthrosis were assessed by Lequesne index (IL) (version 1997) using a valid questionnaire. Neurological examination included the use of the electroneuromyography (EMG).
Results
The patients were divided into two groups depending on the results of motor conduction velocity (MCV) of n. peroneus and sensory conduction velocity (SCV) of nervus suralis. Group 1 consisted of patients with normal MCV/SCV and group 2 – reduced. In group 1 with normal MCV values on n.peroneus more prominent pain associated with inflammatory changes in the knee joints by IL were noted: nocturnal pain in the knee joints was 1.32 ± 0.78 vs 0.81 ± 0.66 points in group 2 ($P = 0.04$), the ability to kneel 1.73 ± 0.46 vs 1.26 ± 0.45 points ($P = 0.01$). In contrast functional disorders (the intensity of pain during the descent one flight of stairs) were more pronounced in group 2 – 1.26 ± 0.45 vs 0.8 ± 0.68 points in group 1 ($P = 0.02$). Reduction of SCV on sensory fibres of n.suralis intensified pain when walking: in group 1 – 0.95 ± 0.40 vs 1.32 ± 0.58 points in group 2 ($P = 0.03$).
Conclusions
DPN was associated with changes in OA pain perception dependent on involvement of motor and sensory fibres. Decreased MCV masked pain associated with inflammatory changes in the knee joints. On the other hand, functional disorders associated with degenerative-dystrophic changes in OA were more marked by damage of both sensitive and motor fibres.

DOI: 10.1530/endoabs.37.EP427

EP428

Lixisenatide clinical experience on patients with type 2 diabetes and obesity in Endocrinology Offices

M Mar Roca-Rodríguez[1], María Teresa Muros de Fuentes[2], Gonzalo Piédrola-Maroto[2], Miguel Quesada-Charneco[3], Silvia Maraver-Selfa[1], M José Tapia-Guerrero[1], Daniel Cepero-García[4], Rosa Orduña-Espinosa[3], Joaquín Pechuán-Asensio[5], Elena Ferrándiz-Millón[4], Purificación Galera-Martínez[2], Mercedes Vázquez-Gutiérrez[4] & Isabel Mancha-Doblas[1]
[1]Department of Endocrinology, Virgen de la Victoria and Regional Hospitals, Malaga, Spain; [2]Department of Endocrinology, Virgen de las Nieves Hospital, Granada, Spain; [3]Department of Endocrinology, San Cecilio Hospital, Granada, Spain; [4]Department of Endocrinology, Torrecardenas Hospital, Almeria, Spain; [5]Endocrinology Private Office, Granada, Spain.

Introduction
Some treatments of diabetes, such as lixisenatide, improve global metabolic status beyond glycaemic control.
Aim
To evaluate tolerance to lixisenatide and its effects on weight and metabolic control in type 2 diabetes and obese patients attended in Endocrinology Offices.
Material and method
A prospective study of patients with type 2 diabetes and obesity. In an intra-subject analysis, clinical and analytical data were evaluated at baseline and after lixisenatide treatment.
Results
We studied 104 patients (51% women) with type 2 diabetes and obesity. Average age was 58.4 ± 10.5 years, average duration of diabetes was 11.2 ± 6.7 years, and 35.6 and 69.6% had family history of cardiovascular disease and diabetes respectively. At baseline, 92.2% of the patients had oral hypoglycaemic agents, 13.5% GLP1 agonists and 67.3% insulin (44.2% basal insulin, 12.5% premixed insulin, and 10.6% basal-bolus insulin). We re-evaluated the patients 3.8 ± 1.6 months after treatment with lixisenatide. We found significant improvements in weight ($P < 0.001$), BMI ($P < 0.001$), WC ($P = 0.002$), SBP ($P < 0.001$), DBP ($P = 0.001$), fasting glucose ($P \leq 0.001$), HbA1c ($P = 0.022$), total-chol ($P < 0.001$), LDL-chol ($P = 0.046$), TG ($P = 0.020$), hypertension drugs ($P < 0.001$), and lipids drugs ($P < 0.001$). We checked that blood pressure and lipid improvement were not due to hypertension and lipid treatment intensification. No changes in levels of amylase related to lixisenatide treatment were observed. Regarding digestive tolerance to lixisenatide, 7.9% of patients did not tolerate, 5% tolerated 10 μg/day, and 85.1% tolerated 20 μg/day.
Conclusions
Significant improvement of anthropometric parameters and glycaemic control in terms of fasting glucose and HbA1c, and significant decrease of blood pressure and lipid profile were observed. Lixisenatide was safety and well tolerated in most patients. In addition, we found a significant intensification of antihypertensive and lipid-lowering therapy, not only hypoglycaemic, in our clinical practice with an overall metabolic approach of patients.

DOI: 10.1530/endoabs.37.EP428

EP429

Nonglycemic effects of incretins in patients with long history diabetes type 1 and chronic kidney disease

Margarita Arutyunova, Alexandra Glazunova, Inna Klephortova, Sergey Martynov, Oxana Manchenko, Irina Ulianova, Alexandr Ilin, Minara Shamkhalova & Marina Shestakova
Endocrinology Research Centre, Moscow, Russia.

Aims
To estimate the nonglycaemic effects of incretins in patients with long history of type 1 diabetes (T1D) and chronic kidney disease (CKD).

Materials and methods
We examined 75 patients with a long history T1D (more than 20 years) and CKD on the different stages: 32 patients with CKD at the stages 1–4, 17 patients on haemodialysis, 11 with kidney transplantation, and 15 patients without CKD. In addition to routine methods of investigation we have estimated mineral and bone disorders (MBD) factors (phosphorus (P), phosphorus and calcium product (PxCa) parathormone (PTH), 25(OH)vitamin D (vitamin D), and fibroblast growth factor 23 (FGF 23)), made a multispiral computed tomography of heart with Agatston index definition. Markers of proinflammatory (monocyte chemoattractant protein-1 (MCP-1) and C-reactive protein (CRP)), fibrosis (transforming growth factor-beta (TGFβ)), and cardiovascular collapse (atrial natriuretic peptide (NTpro-BNP)) were defined. Determining the level of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).
Results
The study showed no difference on the level of GLP-1 and GIP in patients with a long history of T1D, regardless of the presence and stage of CKD and the degree of compensation of diabetes. Received confirmation inverse relationship between GLP-1 and the level of total cholesterol ($r=-0.320$; $P<0.05$), Agatston index ($r=-0.317$; $P<0.05$), as well as the GYP and fibrinogen level ($r=-0.285$; $P<0.05$), CRP ($r=-0.626$; $P<0.05$), FGF-23 ($r=-0.341$; $P<0.05$), and MCP-1 ($r=0.277$; $P<0.05$).
Conclusions
In patients with T1D is defined inhibitory role of incretins in the progression of atherosclerosis and MBD, actively involved in the development of cardiovascular disease, irrespective of the stage of CKD. The obtained data require further study from the standpoint of application nonglycaemic effects of drugs of incretins in the treatment of patients with T1D.

DOI: 10.1530/endoabs.37.EP429

EP430

COMMODITY12 telemedicine system is effective in primary care setting in patients with type 2 diabetes

Krzysztof Lewandowski[1], Maciej Mazurkiewicz[2] & Przemyslaw Kardas[2]
[1]Department of Endocrinology and Metabolic Diseases, The Medical University of Lodz, Lodz, Poland; [2]The First Department of Family Medicine, The Medical University of Lodz, Lodz, Poland.

Background
The COMMODITY12 is a telemedicine system designed for continuous monitoring of diabetes type 1 (DM1) and DM2, as well as the cardiovascular comorbidities. The system has been created in collaboration of nine European academic and industrial partners under FP7 (www.commodity12.eu).
Aim
The aim of this study was to assess clinical utility of the COMMODITY12 system in DM2 patients, under a design of a mini feasibility trial.
Methods
Sixty outpatients from Lodz region (central Poland) with DM2 were randomly ascribed to either control arm ($n=30$), in which they received standard care, or intervention arm ($n=30$), in which they used COMMODITY12 system for daily monitoring of their diabetes-related parameters (glucose level, blood pressure, weight, ECG, heart rate, mobility, a range of lab tests, and adherence to medication). All patients were monitored for a period of 6 weeks. Primary outcome measures was system operability and whole trial feasibility, defined as harmonic technical functioning of all layers of the system, and appropriateness of the personal health system (PHS) for patient use, respectively.
Results
In general, the COMMODITY12 system functioned well, with only some problems with transmission of the data from ECG sensor to the hub. Patients accepted telemedicine system well, and found it to be helpful in self-management of diabetes. System was effective in collecting and analysing data related to both diabetes, and comorbidities (such as hypertension, arrhythmias, or sleep apnoea). In some patients using COMMODITY12 system, trend toward better metabolic control was also observed, as compared to their previous results, as well as to the control group.
Conclusion
These results point at the usefulness of COMMODITY12 system in diabetes care. Further studies on larger groups are warranted to determine the effect of the system on clinical outcomes, as well as its cost-effectiveness.
Disclosure
This Study was a part of the Commodity12 Project (COntinuous Multi-parametric and Multi-layered analysis Of DIabetes TYpe 1 and 2, www.commodity12.eu). EU 7th framework programme.

DOI: 10.1530/endoabs.37.EP430

EP431

Microangiopathic complications in latent autoimmune diabetes in adults: relationship with thyroid autoimmunity

Aura Reghina[1,2], Elisabeta Sava[1], Suzana Florea[1] & Simona Fica[1]
[1]Elias University Hospital, University of Medicine and Pharmacy Carol Davila, Bucharest, Romania; [2]National Institute of Development and Research in Pathology and Biomedical Sciences 'Victor Babes', Bucharest, Romania.

Background
Patients with latent autoimmune diabetes in adults (LADA) are a clinically, immunologically, genetically heterogeneous group and the presence of thyroid autoimmunity (TA) appears to contribute to his heterogeneity.
The aim was to evaluate the impact of TA on microangiopathic complications in LADA patients.
Materials and method
LADA has been defined by the onset of diabetes at ages above 30 years, the lack of need for insulin therapy for at least 6 months after its first appearance, the presence of anti-GAD antibodies (GADA). Positive titers of anti-thyroid peroxidase antibodies (TPOAbs) were observed in 30 (28.8%) out of 104 LADA patients. Prevalence of retinopathy (DR), peripheral neuropathy (PN), autonomic neuropathy (AN), and diabetic nephropathy (DN) were also evaluated.
Results
Patients with TA had twice the risk of RD compared to patients without TA, odds ratios 2.27 (95% CI 0.8–5.7, $P=0.004$). The risk of NP was 1.8 times higher in patients with TA compared with patients without TA (95% CI 0.7–4.4, $P=0.04$). Patients with TA are three times more likely to develop AN than patients without TA, odds ratio 3.4 (95% CI 1–11, $P=0.014$). From ten patients with DN, four of them (40%) had TA compared to 26 patients (27.7%) of 94 without DN. Patients with TA had the probability to develop this complication 1.7 times higher than those without TA, odds ratio 1.74 (95% CI 0.4–6.6, $P=0.46$).
Conclusions
Except diabetic nephropathy, the presence of TA in patients with LADA has determined a significantly higher prevalence of microangiopathic complications.
Acknowledgement
This paper is partly supported by the Sectorial Operational Programme Human Resources Development (SOPHRD), financed by the European Social Fund and the Romanian Government under the contract number POSDRU 141531.
Disclosure
This paper is partly supported by the Sectorial Operational Programme Human Resources Development (SOPHRD), financed by the European Social Fund and the Romanian Government under the contract number POSDRU 141531.

DOI: 10.1530/endoabs.37.EP431

EP432

Evaluation series on safety and efficacy of nutritional supplements (ESSENS) in newly diagnosed hyperglycaemia

Sanjay Kalra
Bharthi Hospital and Research Institute, Karnal, Harayana, India.

Diabetes is endemic in society. Beyond lifestyle modification (often short lived) and metformin, which while effective has gastrointestinal side effects, other available pharmacological options are challenging to implement across populations of newly diagnosed patients. The recent position statement by ADA/EASD calls for patient-centred individualised therapies to suit patients' need. Glucose-lowering nutritional supplements may be an effective and safe option for newly diagnosed hyperglycaemia. But, their safety and efficacy have not been systematically evaluated in randomized clinical trials. In this 12-week, investigator-initiated, six-centre, randomized, double-blind, placebo-controlled, phase 3 trial, newly diagnosed subjects ($n=232$) with FPG >100 mg/dl received PreCrea (a proprietary nutritional supplement containing standardized plant extracts and dietary elements) or placebo one capsule twice daily along with lifestyle modification. Primary endpoint was the change from baseline HbA1c at week 12. Secondary endpoint was change from baseline in FPG. At week 12, HbA1c was significantly reduced from baseline with PreCrea compared to placebo (-0.91 vs $+0.08\%$); $P<0.001$). Reductions in FPG in the PreCrea group compared to placebo (P 0.0428) (-23.1 mg/dl vs -7.2 mg/dl at week 12), with no hypoglycaemia, no weight gain and no adverse effects and no difference in safety parameters. PreCrea provided clinically important and statistically significant improvements in glycaemic control compared to placebo. The efficacy (nearly 1% reduction in HbA1c), safety and tolerability profile of PreCrea

highlights its potential as an initial therapy choice in newly diagnosed hyperglycaemia and in patients intolerant or reluctant to take metformin. Longer head-to-head comparative studies would be required to evaluate efficacy with PreCrea over other oral hypoglycaemia agents in such patients. (ClinicalTrials.gov: NCT02189005; www.essens-study.com).
Disclosure
From PreEmptive Meds, Inc. and Abbott Laboratories.
DOI: 10.1530/endoabs.37.EP432

EP433

Association between cardiovascular disease and microvascular complications in diabetic patients

Gonzalo Allo Miguel, Elena García Fernández, Juan Carlos Romero Rodríguez, Guillermo Martínez Díaz-Guerra & Federico Hawkins Carranza
Endocrinology Service, 12 de Octubre University Hospital, Madrid, Spain.

Introduction
Diabetes mellitus is a condition on the increase, carrying a high risk of cardiovascular complications. It is, also, well known that diabetes confers a substantial burden of microvascular disease. Previous studies suggest a link between microvascular and macrovascular events in diabetes. However, just a few studies have investigated whether the presence of previous cardiovascular events is associated with microvascular disease in diabetes patients. So, this is the aim of our study.
Patients and methods
98 diabetic (48 males/50 females) patients were included. Adverse cardiovascular events were collected, including: myocardial infarction, angina, revascularization, etc. Microvascular complications include: retinopathy, nephropathy and peripheral neuropathy.
Statistical analysis
χ^2 test was used to compare the existence of microvascular complications between the groups with and without cardiovascular events.
Results
68 patients with type 2 and 20 with type 1 diabetes with mean age (52.58 ± 20.70) and mean HbA1c ($11.21 \pm 2.33\%$) were included. 14 patients (15.56%) had previous cardiovascular events. The existence of cardiovascular events was significantly correlated with the existence of, al least, one microvascular complication ($P<0.02$). Also, significant differences between the groups of patients with o without cardiovascular disease were found in the rate of neuropathy (71.43 and 24.66%, respectively, $P<0.001$) and in the rate of nephropathy (57.14 and 23.61%, respectively, $P<0.001$). These differences remained significant after adjusting for age, sex, and hypertension. There were no significant differences in the rate of retinopathy between both groups.
Conclusions
Our results show significant correlation between the existence of previous cardiovascular events and the existence of one or more microvascular complications. Moreover, we have found that diabetic patients with cardiovascular disease present significant higher rates of nephropathy and neuropathy than diabetic patients without cardiovascular events. Despite the limitations of the study, our results suggest that proper microvascular complications screening seems mandatory in diabetic patients with past cardiovascular events.
DOI: 10.1530/endoabs.37.EP433

EP434

Intima–media thickness of internal carotid arteries in the diagnosis of coronary atherosclerosis in patients with type 2 diabetes and silent ischaemia

Larysa Zhuravlyova & Natalia Lopina
Kharkiv National Medical University, Kharkiv, Ukraine.

Aims
To determine the role of intima–media thickness (IMT) of internal carotid artery (ICA) in the diagnosis of coronary atherosclerosis in patients with type 2 diabetes (T2D) and silent ischaemia (SI).
Methods
We provide a retrospective analysis of 60 cases of patients with T2D (24 men, age 60.5 ± 4.7 years), history of diabetes – 4.7 ± 0.5 years. SI was diagnosed by comparing complaints, anamnesis, ECG data and daily ECG monitoring. All patients underwent carotid ultrasound in B-mode to determine the degree of ICA IMT stenosis. The degree of coronary atherosclerosis was evaluated by coronary angiography (CAG).
Results
In 55% of patients with T2D and SI the presence of atherosclerotic lesions of two or three coronary arteries (CA) localised in the middle and distal segments was identified. In 13% of patients with T2D critical subocclusion of CA was found. ICA IMT values were significantly higher in patients with SI and coronary atherosclerosis compared to patients with T2D without atherosclerotic CA lesions (1.41 ± 0.12 vs 1.21 ± 0.11, $P<0.05$), in 20% of patients with T2D and SI the presence of atherosclerotic plaques of ICA was revealed. When conducting multiple logistic regressions in patients with T2D and SI the following predictors of atherosclerotic CA lesions were identified: duration of T2D (OR 4.07, 95% CI 2.56–4.32; $P<0.05$), dyslipidaemia (OR 2.17 95% CI 1.47–3.12; $P<0.05$), gender (OR 1.52, 95% CI 1.14–2.31; $P<0.05$), and ICA IMT (OR 2.81, 95% CI 1.76–3.21; $P<0.05$). AUC value in the analysis of ROC-curve for ICA IMT was 0.75 (95% CI 0.61–0.79; $P<0.05$).
Conclusion
Increased thickness of ICA intima–media and CA atherosclerotic plaques combined with coronary atherosclerosis in patients with T2D and SI should be considered during the screening of this group of patients to identify those to perform CAG and early revascularisation for the prevention of cardiovascular events.
DOI: 10.1530/endoabs.37.EP434

EP435

The relationship between adipokines and diastolic dysfunction in patients with type 2 diabetes mellitus with overweight

Larysa Zhuravlyova & Nelya Sokolnikova
Kharkiv National Medical University, Kharkiv, Ukraine.

The mechanisms of myocardial damage are complex and studied insufficiently in patients with diabetes mellitus type 2 (DM2) with overweight. The contribution of adipokines leptin and resistin into the formation of diastolic dysfunction (DD) in patients with DM2 remains understudied. The purpose of the study was to evaluate the relationship between the state of leptin and resistin activity and DD in patients with DM2 with normal and overweight.
Methods
94 patients with DM2 without systolic dysfunction were randomized into two groups: group 1 ($n=34$) patients with DM2 with a BMI <25 kg/m^2 and group 2 ($n=60$) patients with a BMI >25 kg/m^2. The levels of leptin and resistin were determined by ELISA. Echocardiographic method was performed to measure peak velocity of early diastolic filling flow (peak E), peak velocity of late diastolic filling flow (peak A), the peak E/peak A ratio (E/A), and deceleration time of early diastolic filling (DT).
Results
In group 1 the level of BMI was 24.47 ± 0.52 kg/m^2, leptin 11.76 ± 0.68 ng/ml, resistin 10.17 ± 0.35 ng/ml, the value of the E/A 0.94 ± 0.04, and DT 230.47 ± 3.51 ms. In group 2 the level of BMI was 34.49 ± 0.68 kg/m^2, leptin 22.75 ± 0.49 ng/ml, resistin 14.19 ± 0.18 ng/ml; the value of the E/A 0.81 ± 0.03, and DT 241.72 ± 2.18 ms. In the group 1 a reliable correlation wasn't revealed. In the group 2 a significant correlation was revealed between E/A and leptin ($R=-0.27$ ($P<0.05$)); between DT and leptin ($R=0.35$ ($P<0.05$)); between E/A and resistin ($R=-0.26$ ($P<0.05$)); and between DT and resistin ($R=0.28$ ($P<0.05$)).
Conclusion
Hyperleptinaemia and hyperresistinaemia make a significant contribution to the DD in patients with DM2 with overweight and increase the risk of cardiovascular complications.
DOI: 10.1530/endoabs.37.EP435

EP436

Stroke in prediabetic patients

Julia Silva-Fernández[1], Rafael García-Ruiz[2], Paloma Moreno-Moreno[3], Rosa María García-Ruiz[4] & Carolina González-Pereira[5]
[1]Endocrinology Unit, Mancha Centro General Hospital, Alcázar de San Juan (Ciudad Real), Spain; [2]Neurology Unit, Mancha Centro General Hospital, Alcázar de San Juan (Ciudad Real), Spain; [3]Endocrinology Unit, Reina Sofía University Hospital, Córdoba, Spain; [4]Pedreguer Primary Care Center, Pedreguer (Alicante), Spain; [5]Intensive Care Unit, Central de Asturias University Hospital, Obiedo (Asturias), Spain.

Objective
To describe the clinical characteristics of stroke in patients with prediabetes mellitus (pre-DM) and to compare them with DM and non-DM patient characteristics.
Methods
Retrospective analysis of a prospective series of acute stroke patients. Demographic and clinical characteristics were compared among the three groups, along with outcome data. Stroke severity was evaluated by modified Rankin scale (mRS) and NIHSS (NIH stroke scale).
Results
138 patients (50 non-DM, 32 pre-DM (23%), and 56 DM). Median age was 74.5±15.35, 73.38±13.20, and 73.84±11.44 years respectively. 44% of non-DM, 53.1% of pre-DM and 58.9% of DM patients were men. The prevalence of other vascular risk factors in non-DM, pre-DM, and DM patients was: hypertension (46, 71, and 89%, $^{**}P<0.05$), hypercholesterolemia (42, 65, and 69%, $^{*}P<0.05$), peripheral artery disease (4, 6.2, and 7.1%), and atrial fibrillation (6, 15.6, and 16%). Smoking habit was more common in pre-DM patients (15.6% vs 14% in non-DM patients and 7.5% in DM patients). Stroke characteristics: prevalence of ischemic stroke (IS) was 88% in non-DM patients, 84.3% in pre-DM and 94.6% in DM patients (P 0.24). Transient ischemic attack was more common in non-DM patients (36.3% of IS vs 33.3% in pre-DM and 20.7% in DM patients) (P 0.28). There were no differences in stroke severity between non-DM, pre-DM, and DM patients (4.9±6.2; 4.5±6; and 4.9±5.4 NIHSS median points each group), neither in 3-month mortality (12, 12.5, and 7.1%) and in 3-month mRS (2.18±2.21; 1.81±2.2; and 1.96±1.92). rtPA success rate was 80, 66, and 33% respectively (P 0.91). P (all groups), $^{*}P$ (non-DM/pre-DM patients), and $^{**}P$ (pre-DM/DM patients).
Conclusion
Frequency of pre-DM in higher than observed in general population (10%). Pre-DM patients occupy an intermediate situation regarding vascular risk factors but has no impact on stroke outcomes.

DOI: 10.1530/endoabs.37.EP436

EP437

Diabetes mellitus as a conformational disease: a novel potential therapeutic approach

Isaac Fernández-Gómez[1], Marquiza Sablón-Carrazana[1,2], Alberto Bencomo[1,2], Karina Pasten-Hidalgo[3], Rosa Angélica Castillo-Rodríguez[3], Guadalupe Domínguez[5], Reyna Lara[6], Luis Felipe Jiménez[6], Julio Morán[5], Nelly Altamirano-Bustamante[7], Sergio Islas-Andrade[1], Chryslaine Rodríguez-Tanty[2], Eulalia Garrido-Magaña[4] & Myriam M Altamirano-Bustamante[1]
[1]UIEM, Instituto Mexicano del Seguro Social, Mexico, DF, Mexico; [2]Centro de Neurociencias, Habana, Cuba; [3]Cátedra Conacyt- Instituto Nacional de Pediatría, Mexico, DF, Mexico; [4]Servicio de Endocrinología Instituto Nacional de Pediatría, Mexico, DF, Mexico; [5]Instituto de Fisiología Celular–UNAM, Mexico, DF, Mexico; [6]Facultad de Ciencia–UNAM, Mexico, DF, Mexico; [7]Servicio de Endocrinología, Instituto Nacional de Pediatría, Mexico, DF, Mexico.

Introduction
Type 2 diabetes mellitus is a conformational disease (CD), characterised by deposition (fibrils and cytotoxic oligomers) of the human islet amyloid peptide (hIAPP). CDs have devastating effects on the sufferers and their caregivers, as well as a tremendous economic impact on families and the health system. Novel molecule candidates targeting self-assembled amyloidogenic proteins represent a potential therapeutic approach for CDs.
Methods/design
In this work we carried out a systematic study in order to determine the interrelation between the IAPP and IAPP 20–29 fragments in aggregation kinetic with a novel family of naphthalene compounds, used as chemical chaperones. *N*-(2-aminoethyl)-*N′*-1-naphthylsuccinamide A; methyl (2-((4-(1-naphthylamino)-4-oxobutanoyl)amino)ethyl) dithiocarbamate B; (2R)-2-(6-methoxy-2-naphthyl) propanoic acid (Naproxen) C; *N*-(4-(1-naphthylamino)-4-oxobutanoyl)-β-alanine D; 6-((4-(1-naphthylamino)-4-oxobutanoyl)amino) hexanoic acid E; *N*3,*N*3′-ethane-1,2-dyilbis(*N*1-1-naphthylsuccinamide) F; *N*-(4-aminobutyl)-*N′*-1-naphthyl-succinamide G; and (1E,6E)-1,8-*bis*(4-hydroxy-3-methoxyphenyl)octa-1,6-diene-3,5-dione (Curcumine). We describe the structural features, aggregation kinetics, and toxic properties of the, in presence or absence of a novel naphthalene of the chemical chaperones family.
Results
We found a stronger inhibitory effect in the fibril formation of the chaperones B, C, D, E, and G. Transmission electron microscopy showed the presence of long and curly fibers in the sample control, while the samples treated with chaperones A, B. C, D, and E, generated several amorphous and disaggregated structures. A cytoprotective effect of the chaperones family on cerebellar granule cells was found in the MTT assays. Furthermore, the binding sites of the chemical chaperones to hIAPP were located by means of docking on the IAPP 3D model.
Conclusion
In this study we managed to obtain chaperones that bind to the native state, to the cytotoxic oligomers and the amyloid fibrils. Chaperones derived from naphthalene can regulate fibre formation processes by binding to the native state, minimising the formation of amorphous aggregates, as well as cytotoxic oligomers.
Disclosure
Funding for this study was provided by Mexico's National Council of Science and Technology (CONACYT) SALUD-2010-C02-151942; Cátedras Conacyt and Institute of Science and Technology of Mexico City (ICYTDF).

DOI: 10.1530/endoabs.37.EP437

EP438

Continuous glucose monitoring systems and the improvement in hypoglycaemic awareness post-islet transplantation: a single-centre cohort study

Clare Flood & Shareen Forbes
University of Edinburgh, Edinburgh, UK.

Background
Islet transplantation is an NHS-funded procedure introduced to the UK in 2011 for patients with the most severe type 1 diabetes mellitus (T1DM). These particular patients have unstable blood glucose, frequently occurring episodes of severe hypoglycaemia and impaired awareness of hypoglycaemia (IAH).
Objectives
To evaluate the effectiveness of islet transplantation in improving glycaemic control, reducing the burden of hypoglycaemia and improving awareness of hypoglycaemia through a single-centre cohort study at the Royal Infirmary of Edinburgh.
Methods
A retrospective analysis of data collected over 3 years from the 16 patients who have undergone islet transplantation in Scotland. HbA1c was measured and continuous glucose monitoring systems (CGMS) were utilised to assess glycaemic control, while Gold and Clarke score questionnaires tested IAH.
Results
Glycaemic control significantly improved, as illustrated by percentage time in hypoglycaemia in the months following transplant ($P=0.0211$) and HbA1c ($P=0.0426$). Improved Clarke ($P=0.0034$) and Gold ($P=0.0001$) scores indicate improved glycaemic awareness following transplant.
Conclusion
Our observations in 16 patients suggest that in selected patients, islet transplantation can be a life-changing procedure capable of improving glycaemic control and IAH in select patients with a history of frequent and severe hypoglycaemia. Data can be collated with that from other UK centres to increase statistical power and establish statistical significance for correlation statistics.

DOI: 10.1530/endoabs.37.EP438

EP439

HDL levels is associated with left ventricular ejection fraction in type 2 diabetic patients

Eui-Hyun Kim & Hyun-Ae Seo
Daegu Fatima Hospital, Daegu, Republic of Korea.

Introduction
Considering the high prevalence and significant morbidity and mortality of heart failure in type 2 diabetic patients, identification of risk factors for cardiac

dysfunction is important. The ejection fraction represents how well the heart is pumping out blood and is used to diagnose heart failure. In this study, we investigated the factors associated with left ventricular ejection fraction (LVEF) in type 2 diabetic patients.
Methods
A total of 369 type 2 diabetes patients were included in the present study. We conducted trans-thoracic Doppler echocardiography for evaluating cardiac function. Height, body weight, blood pressure, and biochemical markers were measured for each patient.
Result
The mean age of total patients was 61.24 ± 12.27. The mean LVEF was $58.63 \pm 9.15\%$. In total patients, HDL was significantly positively correlated with LVEF ($r=0.163$, $P=0.002$). This significant association was retained in multivariate analysis adjusted for age, BMI, creatinine, haemoglobin, and presence of hypertension ($r=0.164$, $P=0.003$). In order to rule out the possibility of increasing LVEF due to diastolic heart failure, we performed subgroup analysis. In patients with type 2 diabetes who have normal diastolic function, LVEF and HDL was significantly positively correlated ($r=0.246$, $P=0.013$). Triglyceride (TG) was significantly negatively associated ($r=-0.217$, $P=0.029$). After adjusted by age, BMI, creatinine, haemoglobin, and presence of hypertension, the positive correlation between LVEF and HDL was retained ($r=0.206$, $P=0.045$). TG was not associated with LVEF after adjustment ($r=-0.089$, $P=0.393$).
Conclusion
In the present study, we found that HDL level is significantly associated with LVEF in type 2 diabetic patients with or without diastolic heart failure. This suggests that the treatment for raising HDL might have a role in the improvement of heart function in type 2 diabetic patients.

DOI: 10.1530/endoabs.37.EP439

EP440

Low testosterone and erectile function in male patients with type 2 diabetes

Vitaliy Luchytskiy & Eugen Luchytskiy
SE 'Institute of Endocrinology and Metabolism named after V.P. Komissarenko National Academy of Medical Science of Ukraine', Kyiv, Ukraine.

Erectile dysfunction (ED) – frequent disease that accompanies diabetes or is its complication. According to various reports the prevalence of ED in males with type 2 diabetes (T2DM) varies from 25 to 90%. In recent years, the ED is considered as predict factor in the development of T2DM in men and as a marker of vascular complications progression.
Aim
To examine the state of androgens in men suffering from T2DM and erectile dysfunction.
Material and methods
We observed 205 male patients (48 ± 4.6 years) with T2DM (HbA1c did not exceed 6.5%) with complaints on ED. Erectile function was determined with international index of erectile function scale. Levels of total testosterone (tT), estradiol (E_2), and LH in blood serum were measured with immunoferment method. The controls – 24 healthy men without diabetes and ED (25–58 years).
Results
The average index of erectile function scored 17.23 ± 2.08 points and was lower than in the controls – 26.75 ± 0.79 ($P<0.01$). Satisfaction with sexual intercourse was reduced compared with the controls (9.34 ± 0.93 vs 16.18 ± 0.68 points ($P<0.01$). Orgasmic feelings and sexual desire were lower in T2DM patients than is controls (6.48 ± 0.72 vs 9.23 ± 0.26 points ($P<0.05$) and 9.44 ± 0.95 vs 13.93 ± 0.56 points ($P<0.01$) respectively). The index of erectile function in T2DM patients studied showed moderate ED in 62.4% cases (15.1 ± 0.68) and severe ED in 22.4% of patients (12.2 ± 0.44). Levels of tT in group 41–50 years was 3.1 ± 0.47 ng/ml, 51–60 years was 2.7 ± 0.71 ng/ml, and >60 years was 2.9 ± 0.55 ng/ml vs 5.63 ± 0.9 ng/ml and were lover than in control (5.63 ± 0.9 ng/ml). Serum levels of E_2 in patients did not differ from the controls (0.17 ± 0.04 pmol/l vs 0.14 ± 0.02 pmol/l), as well as LH concentrations (4.28 ± 0.36 IU/l vs 4.2 ± 0.5 IU/l).
Conclusions
Low testosterone is an important pathogenic factor in the development of ED in men with T2DM.

DOI: 10.1530/endoabs.37.EP440

EP441

Glargine insulin treatment during pregnancy in type 1 diabetes mellitus

Paloma Moreno-Moreno, Rafael Palomares-Ortega, Concepción Muñoz-Jiménez & María Ángeles Gálvez-Moreno
Management Unit of Clinical Endocrinology and Nutrition, University Hospital Reina Sofía, Córdoba, Spain.

Objective
The aim of this study was to evaluate maternal and neonatal outcomes in women with type 1 diabetes mellitus (DM1), and analysing differences associated to insulin glargine exposure during pregnancy.
Patients and methods
Retrospective descriptive study of pregnancies in women with DM1 (2004–2012). Variables analysed: baseline characteristics (age, time of diabetes evolution, microvascular complications, and weight), maternal outcomes (weight gain, HbA1c, hypoglycaemia, preeclampsia, abortions, and vaginal delivery and caesarean section) and neonatal outcomes (gestational age at delivery, birth weight, and congenital malformations). The pregnancies were divided in groups attending to their exposition to glargine insulin and were analysed to evaluate possible differences between them (group 1: exposed and group 2: unexposed).
Statistical analysis
Comparing proportions with the χ^2 and comparing means with Student's *t*-test.
Results
132 pregnancies in women with DM1. Group 1: 57 (43.2%) and group 2: 75 (56.8%). Baseline characteristics were similar in both groups. HbA1c was different before pregnancy (group 1 vs group 2: 7.95% vs 7.02%; $P=0.001$), but similar during pregnancy (group 1 vs group 2: first trimester 6.83% vs 6.47%; second trimester 6.45% vs 6.33%; and third trimester 6.67% vs 6.42%; $P>0.05$). Maternal weight gain was similar in both groups (group 1 vs group 2: 10.28 kg vs 11.02 kg, $P=0.4$). Maternal and neonatal outcomes (group 1 vs group 2): abortions 1 (2%) vs 9 (12%), $P=0.05$; caesarean section 18 (31.5%) vs 39 (52%), $P=0.005$; gestational age at delivery 38.02 weeks vs 38.12 weeks, $P=0.93$; macrosomia 13 (23%) vs 21 (28%), $P=0.29$; congenital malformations 3 (23%) vs 6 (28%), $P=0.49$; and neonatal hypoglyceamia 1 (2%) vs 5 (7%), $P=0.13$.
Conclusions
The number of caesarean sections was higher in women not exposed to insulin glargine. Insulin glargine use before and during pregnancy is not associated with worse maternal and neonatal outcome, or congenital malformation.

DOI: 10.1530/endoabs.37.EP441

EP442

Hemorheological alterations in type 2 diabetes patients with nephropathy

Min Young Lee, Sehee Jo, Min Jin Kim, Ji Sun Nam, Shinae Kang, Jong Suk Park, Chul Woo Ahn & Kyung Rae Kim
YUMC, Seoul, Republic of Korea.

Background
Hemorheologic alterations or changes in blood viscosity have been suggested to play a role in the pathogenesis of diabetic microvascular complications. We measured various hemorheologic parameters in type 2 diabetes patients at different stages of chronic kidney disease (CKD) and assessed their possible role as early markers of diabetic nephropathy and renal insufficiency.
Methods
One hundred and five patients with type 2 diabetes were divided into four groups according to glomerular filtration rate (GFR). Hemorheologic parameters, including erythrocyte deformability, fibrinogen/elongation index (EI), and aggregation index (AI) were measured using microfluidic hemorheometer. Various metabolic parameters were assessed from fasting blood samples and urine albumin/creatinine ratio (ACR) was calculated from first morning voided urine.
Results
There were significant differences in RBC deformability, AI, critical stress, fibrinogen/EI, and albumin/creatinine ratio among patients in different stages of CKD (all $P<0.05$), RBC deformability and fibrinogen/EI significantly differed between normal and CKD 2 patients while there was no such difference in ACR. In multiple regression analysis, fibrinogen/EI at 3Pa was an independent predictor of GFR ($\beta=-0.328$, $P<0.05$). Also, AI, critical stress, and fibrinogen/EI were significantly different among patients at different stages of diabetic nephropathy, with a significant difference in fibrinogen/EI between normal and microalbuminuric patients (all $P<0.05$).
Conclusions
RBC deformability and fibrinogen/EI are sensitive parameters measured via point-of-care testing for detecting erythrocyte alterations in early CKD and

nephropathy in patients with type 2 diabetes. Further studies are warranted to verify their use as screening tools for diabetic nephropathy and renal impairment.
Disclosure
This study was supported by a grant of the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI12C0122, 2012).
DOI: 10.1530/endoabs.37.EP442

EP443

Impact on quality of life in peoples with painful diabetic peripheral neuropathy

Chong Hwa Kim[1], Su Jin Jeong[1], Ji Oh Mok[2], Ki Young Lee[3] & Sung Rae Kim[4]
[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Sejong General Hospital, Bucheon, Republic of Korea; [2]Division of Endocrinology and Metabolism, Department of Internal Medicine, Soon Chun Hyang University Bucheon Hospital, Bucheon, Republic of Korea; [3]Division of Endocrinology and Metabolism, Department of Internal Medicine, Gacheon University Gil Hospital, Incheon, Republic of Korea; [4]Division of Endocrinology and Metabolism, Department of Internal Medicine, Bucheon St. Mary's Hospital, The Catholic University of Korea, Bucheon, Republic of Korea.

Objective
This study was performed to determine the impact on quality of life and sleep impairment of painful diabetic peripheral neuropathy (PDPN).
Research design and method
The study pool consisted of 200 randomly selected peoples with type 2 diabetic peripheral neuropathy. PDPN was diagnosed using visual analogue scales (VAS) and medical history. The patients were asked to answer the Brief Pain Inventory-Short Form (BPI-SF), Medical Outcomes Study Sleep (MOS-Sleep) Scale, EuroQol (EQ-5D), and VAS and estimate the quality of life in people with diabetic peripheral neuropathy.
Results
Among the patients with diabetic peripheral neuropathy ($n=200$), 82 (41%) were diagnosed with PDPN. PDPN was independently associated with age, fasting plasma glucose, hypertension, dyslipidaemia, and previous cerebrovascular events. All pain severity and interference measures were higher in patients with PDPN than those in patients with painless DPN and patients with PDPN reported more impaired sleep and lower EQ-5D and VAS scores. 200 patients had DPN and Pain Severity Index and pain interference items such as general activity, mood, walking, normal work, relationship, sleep, and enjoyment of life in BPI–DPN were higher in patients with painful DPN compared to those in patients with painless DPN. MOS 6 items-sleep adequacy, respiratory problem during sleep, sleep initiation problem, sleep maintenance problem, and somnolence-sleep scale were lower in patient with painful DPN than painless DPN. EQ-5D index were lower in patients with painful DPN compared to those in patients with painless DPN.
Conclusions
Patients with painful DPN have greater discomfort during daily activities and sleep, and reduced QoL compared to patients with painless DPN. This study provides on the extent of the impact of pain on QoL in patients with painful DPN and physicians should carefully consider pain symptoms in patients with diabetic peripheral neuropathy.
DOI: 10.1530/endoabs.37.EP443

EP444

Prevalence and management of peripheral diabetic neuropathic pain in a hospital diabetes clinic: how are we doing?

Anna Haley & Parijat De
Department of Diabetes and Endocrinology, City Hospital, Birmingham, UK.

Introduction
Peripheral diabetic neuropathic pain (PDNP) as a significant complication of diabetes mellitus (DM), which is present in 16–26% of patients. NICE UK guidelines recommend that physicians should make an formal enquiry about distressing neuropathic symptoms annually and that either duloxetine, amitriptyline, gabapentin, or pregabalin should be used as first-line treatment for neuropathic pain.
Aims
To assess the prevalence PDNP in a diabetic cohort and whether management was according to NICE guidelines. Patients attending an outpatient clinic in SWBH, Birmingham were prospectively consented to answer questions regarding sensations in their feet and lower legs using an adapted and validated questionnaire from the 'Lily Toolkit' and validated 'S-LANSS score' for identifying pain of neuropathic origin.
Results
A total of 100 patients (July–Oct 2014) agreed to answer questions, of which 65% were males (average age 62 years). 98% of patients had an annual foot check: via GP (88), podiatrist (6), or hospital specialist (4), with formal assessment of their ulcer risk but did not include questions about painful neuropathy. 27% ($n=27$) patients admitted getting pain in their feet or lower legs, which was consistent with PDNP. The average pain score in this group was seven out of ten and two-thirds had spoken to a healthcare professional about their symptoms in the past. Of these, 5/27 (19%) were on one of the recommended medications for PDNP; amitriptyline ($n=1$), gabapentin ($n=2$), and combined amitriptyline and gabapentin ($n=2$).
Discussion
In this diabetic cohort, foot checks with respect to ulcer risk were reliably undertaken by the GP. However, 27% of patients had symptoms consistent with PDNP but nearly 79% weren't on any of the first line treatments recommended by NICE. Would incorporation of questions about symptoms of PDNP into the annual primary care foot checks improve the detection rates and subsequently the management of these patients?
DOI: 10.1530/endoabs.37.EP444

EP445

The effect of metformin on spontaneous apoptosis in patients with type 2 diabetes

Aleksandra Panchenko, Kondratska Iryna & Mankovsky Boris
P.L. Shupyk National Medical Academy of Post-graduate Education, Kiev, Ukraine.

Today, there are 382 million people living with diabetes. The overwhelming majority have a type 2 diabetes. Metformin is first-line drug is for many of them.
Materials and methods
The study involved 26 patients in mean age 54.46 ± 1.2 years (from 41 to 65), among them, 14 women and 12 men. 21 patients with newly diagnosed diabetes and five patients receiving treatment with sulfonylureas. All patients were prescribed metformin in mean dose 2000 mg. During the study were determined the levels of HbA1c and spontaneous apoptosis before and after treatment. Measurement of apoptosis were performed by flow cytometry.
Results

Showing	Before treatment ($n=26$)	After treatment ($n=26$)
HbA1c (%)	8.34 ± 0.24	7.57 ± 0.22*
Spontaneous apoptosis (%)	15.9 ± 1.7	11.8 ± 1.2*

Significant difference between the indices before and after treatment (*$P<0.05$). Analysing the results obtained in the groups of patients a significant decrease in HbA1c and a significant decrease in spontaneous apoptosis.

Conclusions
Metformin in the treatment of diabetes mellitus leads to a decrease in blood glucose and compensation of diabetes. And also metformin reduces the level of spontaneous apoptosis. However, studies of mitochondrial changes membrane potential revealed statistically ($P<0.05$) significant reduction cells with signs of apoptosis $15.9 \pm 1.7\%$–$11.8 \pm 1.2\%$ after 90 days of therapy. It the increase in mitochondrial activity and resistance MNCs that turn points to restore energy components of blood cells. And no changes on indicators of surface markers indicating exactly on stimulatory effect of therapy.
DOI: 10.1530/endoabs.37.EP445

EP446

Microalbuminuria by concentration serum and urine levels of adropin in patients with type 2 diabetes mellitus

Kader Ugur[1], Burak Oz[3], Yusuf Ozkan[1], Selcuk Yusuf Sener[1], Bedrettin Orhan[3] & Suleyman Aydin[2]
[1]Department of Endocrinology, Faculty of Medicine, First University, Elazig, Turkey; [2]Department of Biochemistry, Faculty of Medicine, First University, Elazig, Turkey; [3]Department of Internal Medicine, Faculty of Medicine, First University, Elazig, Turkey.

Introduction
Diabetes mellitus is an important public health problem due to defects of the effect of the insulin or insulin deficiency, accompanied by chronic microvascular complications with diabetic nephropathy is characterised by proteinuria that the increasing number of patients progress to end stage renal disease. Many peptide hormone made in etiopathogenesis is situated, although adropin which discovered in recent years involves in glucose homeostasis, its relation to diabetes and nephropathy has still not been investigated. Thus, in this research, the determining of serum and urine levels of adropin in diabetic patients, the relationship between adropin and diabetes mellitus with diabetic nephropathy were aimed to investigate.
Methods
The serum and urine levels of adropin in 20 healthy individuals to form a control group with total of 60 diabetic patients including normoalbuminuric 20, microalbuminuric 20, and overt albuminuric 20 ones were measured.
Results
Serum adropin levels compared with the overt albuminuric group were significantly as lower in healthy control, normoalbuminuric, and microalbuminüric groups (respectively; $P=0.007$, $P<0.001$, and $P=0.008$). Adropin were found to be positively correlated with serum creatinine and microalbuminuria levels (respectively; $P=0.031$, $r=0.242$ vs $P=0.001$, $r=0.379$). Adropin urine levels were significantly as higher in diabetic patients than in healthy controls ($P=0.001$). Compared with the normo and overt albuminuric groups, adropin urine levels were lower in microalbuminuric group ($P=0.026$ for both).
Discussion
As a result, the serum adropin levels appear to be increased in overt albuminuric group. The cause of increased activity of these peptides associated with endothelial function and energy homeostasis can be considered for renal hemostasis. Urinary adropin levels to be lower only in the diabetic microalbuminuric group, can be identified triggering factor clinically at the initial phase of diabetic nephropathy due to the fact that a peptide hormone.

DOI: 10.1530/endoabs.37.EP446

EP447

Abstract unavailable.

DOI: 10.1530/endoabs.37.EP447

EP448

Remitting seronegative symmetrical synovitis with pitting oedema syndrome in association with saxagliptine: case report

Muge Bilge[1], Mine Adas[1,2], Aysen Helvaci[1] & Recep Yilmaz Bayraktarli[1,3]
[1]Internal Medicine, Okmeydani Education and Research Hospital, Istanbul, Turkey; [2]Endocrinology, Okmeydani Education and Research Hospital, Istanbul, Turkey; [3]Radiology, Okmeydani Education and Research Hospital, Istanbul, Turkey.

Background
Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE syndrome) is a very rare clinical entity including a tenosynovitis of the hands and wrists, and marked pitting oedema on upper and lower extremities. RS3PE has been suggested to be associated with many disease conditions and drugs. Saxagliptine is DPP4 inhibitor that relatively new oral hypoglycaemic agent. This case is the second report of the occurrence of RS3PE in patients receiving a DPP4 inhibitor.
Case
A 51-year-old man presented with bilateral hand oedema. The symptoms onset within after initiating saxagliptine of the treatment. He had type 2 diabetes mellitus (HbA1c = 6.6%), and hyperlipidaemia. At the time of presentation, his other medications were metformin, premixed insülin (aspart and protamine), and rosuvastatine. He did not have any history of drug allergy or systemic rheumatic illness. Physical examination revealed tenosynovitis characterized by swelling and moderate tenderness of the metacarpophalangeal and proximal interphalangeal joints bilaterally. There was marked non-tender pitting edema on the dorsum of both hands and wrist joints. Physical exam results were otherwise normal. Laboratory evaluation revealed normal ESR, and negative ANA, ANCA, RF, and ACPA. X-rays and MRI revealed only soft-tissue swelling without evidence of joint destruction. Owing to the absence of complete remission with removal of saxagliptine during the 4 weeks, saxagliptine was tought to be responsible for the aetiology of RS3PE syndrome. Than patient was treated with prednisone 20 mg daily. Clinical findings were dramatic response to prednisone.
Conclusions
This case demonstrates a possible direct aetiological link between saxagliptine and RS3PE.

DOI: 10.1530/endoabs.37.EP448

EP449

Effects of dietary nitrate on metabolic status and myocardial ischaemia–reperfusion injury in type 2 diabetic rats

Asghar Ghasemi[1], Sajad Jeddi[1], Saeedeh Khalifi[2], Mahboubeh Ghanbari[2], Ali Rahimipour[2] & Faranak Kazerouni[2]
[1]Research Institute for Endocrine Sciences, Endocrine Physiology Research Center and Endocrine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [2]Department of Medical Laboratory Sciences, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Introduction
Considering the protective effects nitrate has against diabetes and cardiovascular diseases, we aimed to determine effects of dietary nitrate on metabolic status and myocardial ischemia–reperfusion (IR) injury in type 2 diabetic rats.
Methods
Rats were divided into four groups ($n=7$): control, control + nitrate, diabetes, and diabetes + nitrate. Diabetes was induced by nicotinamide + streptozotocin, and nitrate added to drinking water (100 mg/l) of animals for 2 months. Serum nitrate + nitrite (NOx), glucose, lipid profile, total antioxidant capacity (TAC), catalase (CAT) activity, and systolic blood pressure (SBP) were measured before and after the study. After 2 months, i.v. glucose tolerance test was performed and hearts were perfused by Langendorff apparatus; before and after IR, LVDP, and $\pm$dp/dt, and heart levels of malondialdehyde (MDA) and NOx were measured.
Results
Diabetic rats had lower serum NOx values compared to baseline (29.2 ± 5.6 µmol/l vs 39.0 ± 3.2 µmol/l, $P<0.05$), which normalized after nitrate therapy. Serum glucose in the diabetes + nitrate group was less increased, than the diabetes one (24.1% vs 90.2%; $P<0.05$). Nitrate therapy in diabetic rats significantly improved glucose tolerance and decreased serum cholesterol, LDL-C, and triglycerides by 22.9, 54.2, and 47.6% respectively and increased serum HDL-C by 42.4% compared to baseline. Diabetic rats had lower TAC and CAT activity, which normalized after dietary nitrate therapy. Recovery of LVDP and + dp/dt were 15 and 17% lower in diabetic rats vs controls respectively, but almost normalized after dietary nitrate, which also restored elevated SBP to near normal status (131.2 ± 4.4 vs 120.6 ± 2.2). Compared to controls, heart NOx level was lower in diabetic rats before IR, but was higher after. Diabetic rats had higher MDA levels both before and after IR, which along with heart NOx levels stabilized following dietary nitrate.
Conclusions
Nitrate therapy improved glucose tolerance, restored dyslipidaemia, prevented increase in SBP, and provided cardioprotection against IR injury in diabetic rats.
Disclosure
This work was supported by the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences (grant numbers 498 and 711) and Department of Medical Laboratory Sciences, Faculty of Paramedical Sciences, Shahid Behesht.

DOI: 10.1530/endoabs.37.EP449

EP450

The influence of erythropoietin therapy on serum level of tumour necrosis factor alpha in anaemic patients with early stages of diabetic nephropathy

Ivan Pchelin & Alexander Shishkin
St. Petersburg State University, St. Petersburg, Russia.

Aims
Anaemia occurs early and predicts high risk of cardiovascular events and death in patients with diabetic nephropathy. In our previous studies we have shown that haemoglobin level has a negative correlation with serum levels of proinflammatory cytokines in this clinical group. It could be hypothesised that treatment of anaemia has anti-inflammatory effects. The aim of this study was to assess the influence of treatment with erythropoietin alpha on serum level of tumour necrosis factor alpha (TNFα) in patients with early diabetic nephropathy.
Methods
We included 36 patients with type 2 diabetes mellitus and early diabetic nephropathy (CKD stages 1–3) complicated with anaemia. Patients with non-renal causes of anaemia and/or iron overload were not included. The main group (17 patients) received erythropoietin alpha subcutaneously (starting from 30 IU/kg with further correction of dose according to NKF-K/DOQI Guidelines, 2006) and iron medication orally (ferrous sulphate, 200 mg/day) for 16 weeks. The control group (19 patients) received only oral iron medication (ferrous sulphate, 200 mg/day) for the same period of time. Besides performing routine clinical tests we measured serum concentrations of TNFα using EIA before and after 16 weeks of treatment. Mann–Whitney *U* test was used to compare mean levels of TNFα in study groups. Wilcoxon's test was used to assess dynamics of this parameter during treatment in each group.
Results
Before treatment we found no difference in mean serum levels of TNFα in clinical groups: main group – 30.8 ± 4.5 pg/ml, control group – 27.5 ± 3.9 pg/ml (reference value <50 pg/ml). After 16 weeks of treatment both groups had no significant changes in concentrations of TNFα as compared to initial values. Mean serum levels of TNFα were as follows: main group – 25.0 ± 3.6 pg/ml, control group – 31.1 ± 4.2 pg/ml ($P>0.05$ for the difference between studied groups).
Conclusion
The results of the study suggest that neither treatment with iron sulphate nor comprehensive antianaemic therapy with erythropoietin alpha and iron medication don't lead to a reduction in serum concentration of TNFα in anaemic patients with early stages of diabetic nephropathy.

DOI: 10.1530/endoabs.37.EP450

EP451

Metabolic status in patients with type 1 diabetes mellitus

Elena Vashchenko
The Republican Research Centre for Radiation Medicine and Human Ecology, Gomel, Belarus.

Objective of the study was to analyse the relationship of compensation, lipid profile parameters and androgenic status in patients with type 1 (DM1) depending on the duration of diabetes. There were examined 76 men with DM1 aged 20–49 years (mean age 35.8 ± 8.2) and duration of diabetes more than a year. The control group consisted of 25 healthy men aged 21–41 years (mean age 34.6 ± 7.8). Compensation of diabetes was assessed by the level of HbA1c. Also there were assessed the lipid profile parameters (total amount of cholesterol and triglycerides), total testosterone, FSH, LH, prolactin hormone, sex hormone binding globulin, and homocysteine. Statistical analysis of the data was performed using the software package Microsoft Exel 2003 (SPSS 17.0).

It has been determined that at the absence of compensation in patients with DM1 (HbA1c $8.3 \pm 1.4\%$), with the increasing duration of diabetes there was noticed the increasing of BMI: a group with DM <10 years, 24.6 ± 3.9 kg/m^2, the group with DM >10 years, 27.6 ± 4.4 kg/m^2 ($P=0.01$), progression of lipid storage disease (increased level of triglycerides: 1.4 ± 1.1 mmol/l vs 3.7 ± 1.3 mmol/l in the group with DM >10 years ($P=0.01$)). We were not found the difference in levels of total cholesterol, LH, FSH, prolactin hormone, sex hormone binding globulin, and homocysteine. The absence of androgenic status disorders and changes of homocysteine level are probably associated with the young age of patients, a slight excess of weight and a lack of decrease in GFR. The detected changes are important risk factors of development and progression, and require appropriate arrangements, including the correction of body weight and secondary dyslipidaemia.

DOI: 10.1530/endoabs.37.EP451

EP452

The effect of exenatide treatment on serum ghrelin levels in patients with type 2 diabetes

Figen Topyildiz[1], Sinem Kiyici[1], Zulfiye Gul[2], Deniz Sigirli[3], Metin Guclu[1], Gurcan Kisakol[1] & Sinan Cavun[2]
[1]Department of Internal Medicine, Sevket Yilmaz Education and Research Hospital, Bursa, Turkey; [2]Department of Pharmacology, Medical Faculty, Uludag University, Bursa, Turkey; [3]Department of Bio-Statistics, Medical Faculty, Uludag Univesity, Bursa, Turkey.

Aim
Ghrelin plays an important role in stimulation of food intake and long-term regulation of body weight. In present study we aimed to investigate the effect of exenatide treatment on serum ghrelin levels in patients with type 2 diabetes.
Methods
Fourteen women patients with type 2 diabetes treated with metformin and exenatide were enrolled in the study. A mixed meal test was applied to the patients while they were using their daily medications. Serum total ghrelin, glucose and insulin levels were investigated at baseline (0th min) and at the 60th, 120th, and 180th min after a mixed meal test. On the following week exenatide treatment of the patients was paused for 24 h and the same experimental procedures were repeated.
Results
Serum ghrelin levels were found suppressed significantly at the 60th and 180th min compared with baseline values after mixed meal test with exenatide treatment ($P=0.042$ and $P=0.000$ respectively). While percentage change in serum ghrelin levels after mix meal tests with and without exenatide usage were compared, no significant difference was found at the 60th and 120th min. But percent changes in serum ghrelin levels at the 180th min was statistically significant ($P=0.001$).
Conclusions
In present study we found that exenatide treatment suppresses serum ghrelin levels for longer time compared with the results of skipped exenatide treatment. These results suggest that the effect of exenatide on weight loss may be related with prolonged suppression of serum ghrelin levels, which is an orexigenic peptide.

DOI: 10.1530/endoabs.37.EP452

EP453

The effect of compensation of diabetes on ulcer healing in patients with diabetic foot syndrome

Maksym Prystupiuk
Bogomolets National Medical University, Kyiv, Ukraine.

Introduction
Diabetic foot syndrome is a common surgical pathology. It is the main cause of lower limb amputations, which can be avoided in 85% of cases by active detection and long-term compensation of T2DM, timely diagnostics of peripheral neuropathy.
Purpose
To study relation between compensation of diabetes (by HbA1c) and time needed for healing of ulcers and purulent processes in patients with neuroischaemic forms of diabetic foot.
Results
The results of treatment of 363 patients were worked out: 164 males (45%) and 199 females (55%), the average age of men 65 ± 0.20 years, women 70 ± 0.22 years ($P<0.001$). By admission, patients had been treated by oral hypoglycaemic medicines in combinations of up to three drugs at the time with maximum permissible doses. In hospital all subjects were treated with insulin. The most common surgery was opening of abscesses and phlegmons in 40% of males and 60% of females. Amputations of lower limbs and phalanges were performed in 40% of men (over 66 years) and 20% of women (over 70 years). In terms of post-prandial glycaemia, compensation of diabetes was achieved in 22% of males and 32% of females, stay period in hospital of whom was the lowest.
Conclusions
i) With HbA1c $15.5 \pm 1.0\%$, duration of treatment of neuroischaemic forms of diabetic foot lasted 34.66 ± 0.40 days for males and 31.42 ± 1.18 days for females, while with HbA1c $12.6 \pm 1.2\%$ it lasted 16.60 ± 0.26 and 18.95 ± 0.51 days respectively. ii) Fasting glycaemia up to 6 mmol/l and post-prandial glycaemia up to 10 mmol/l are the best values for enhancing reparative processes in patients and shortening their hospital stay. iii) Among patients with uncompensated diabetes, number of limb amputations is so high that this should motivate patients for conducting adequate treatment and self-control of diabetes.

DOI: 10.1530/endoabs.37.EP453

EP454

Lixisenatide improves glycaemic control and body composition in uncontrolled type 2 diabetic patients treated with insulin

Florentino Carral, Carmen Ayala, Antonia Piñero, Ana Isabel Jiménez, Coral Exposito & Concepción García
Endocrinology Department, Puerto Real University Hospital, Puerto Real, Cádiz, Spain.

Objective
Evaluate the efficacy and safety of adding lixisenatide to uncontrolled type 2 diabetic (T2DM) patients treated with insulin.
Methods
A prospective uncontrolled study was designed. Primary endpoints (measured at 3 and 6 months) were change in HbA1c, weight, and insulin doses. Variables analysed were: HbA1c level, insulin and other hypoglycaemic agents doses, capillary glucose tests, number and type of hypoglycaemias, side effects and body composition analysis (Tanita SC-330).
Results
Data from 42 T2DM patients (55% women; mean age: 57.7 ± 7.4 years; and T2DM duration: 13.5 ± 8.7 years) treated with insulin were analysed. A significant decrease in HbA1c levels (7.6 ± 0.8% vs 7.8 ± 1.1% vs 9.1 ± 1.6%; $P < 0.001$) and weight (95.2 ± 14.8 kg vs 95.8 ± 14.4 kg vs 98.5 ± 13.9 kg) was observed at 3 and 6 months compared to baseline and % of fat mass had also reduced at 6 months (33.9 ± 7.6% vs 38.8 ± 8.1%; *P*: 0.01). Total insulin doses decreased from baseline (61.2 ± 37.3 UI/day) to 3 (52.5 ± 34.8 UI/day; *P*: 0.02) and 6 months (49.4 ± 30.5 UI/day; *P*: 0.021). Low incidence of no serious hypoglycaemias (1.0 ± 1.7 mean episodes/month) was referred. Six patients (14.2%) discontinued lixisenatide treatment due to side effects (four patients for nausea or vomiting, one patients for hypertransaminasemia, and one patient for uncontrolled hyperglycaemia). Three patients (7.1%) were lost to follow-up for unknown reasons.
Conclusions
In our clinical experience, lixisenatide contributes to improving glycaemic control as facilitates weight loss and insulin doses reduction in T2DM patients uncontrolled with insulin.

DOI: 10.1530/endoabs.37.EP454

EP455

Liraglutide improves β-cell function, measured by the C-peptide/glucose ratio, in obese patients with type 2 diabetes

Ana M Ramos-Leví[1] & Miguel A Rubio[2]
[1]Department of Endocrinology and Nutrition, Instituto de Investigación Princesa, Hospital Universitario Princesa, Universidad Autónoma, Madrid, Spain; [2]Department of Endocrinology and Nutrition, Instituto de Investigación San Carlos, Hospital Clínico San Carlos, Universidad Complutense, Madrid, Spain.

Introduction
β-cell function declines progressively in patients with type 2 diabetes (T2D). the fasting C-peptide/glucose ratio (Cp/G) is used for its evaluation. The GLP1 receptor agonist liraglutide improves glucose and weight control, presumably due to improvement of β-cell function and/or mass. This study evaluates the effect of a 6-months' treatment with liraglutide in β-cell function, measured by Cp/G, in patients with obesity and T2D.
Materials and methods
We analysed 43 patients (24 women) with orally treated T2D and obesity, to whom liraglutide 1.2 mg/day was added. At 3 months, liraglutide was increased to 1.8 mg/day if HbA1c or weight goals were not fully achieved. We evaluated clinical and analytical data before and after a 6-months' treatment. Cp/G was used to assess β-cell function.
Results
Basal characteristics before liraglutide (mean ± S.D.): BMI 39.3 ± 4.9 kg/m^2, T2D duration 6.7 ± 3.8 years, fasting glucose (FG) 149.8 ± 36.9 mg/dl, HbA1c 7.6 ± 0.8%, HOMA 6.1 ± 3.3, and Cp/G 0.0261 ± 0.0103. 26 (60.5%) patients previously received one oral-hypoglycemic-agent (OHA), and the rest, two. At 3 months, dosage was increased to 1.8 mg/day in 24 (55.8%) cases; these patients had higher pre-treatment HbA1c (7.8 ± 0.9% vs 7.3 ± 0.7%, $P = 0.025$) and lower Cp/G (0.0235 ± 0.0099 vs 0.0295 ± 0.0101, $P = 0.057$), compared to those who remained on 1.2 mg/day. After 6 months of liraglutide, BMI 37.3 ± 5.2 kg/m^2, percentage weight loss (%WL) 5.2 ± 4.8 kg, FG 132.5 ± 47.3 mg/dl, HbA1c 6.8 ± 1.2%, and HOMA 4.8 ± 3.2 ($P < 0.05$ in all cases). Cp/G at 6 months increased 15.4 ± 36.6%, reaching 0.0296 ± 0.0148 ($P = 0.047$), regardless of pre-treatment HbA1c or final dosage of liraglutide. Pre-treatment Cp/G correlated with %WL ($r = 0.310$, $P = 0.043$) and HbA1c at 6 months ($r = -0.482$, $P = 0.001$) . Decrease of HbA1c and %WL were similar regardless of pre-treatment HbA1c, BMI, or Cp/G. Individuals with pre-treatment Cp/G within the lower quartile achieved 6-month HbA1c levels <7% less frequently.
Conclusions
Liraglutide seems to improve β-cell function, measured by Cp/G, after 6 months, regardless of basal BMI, HbA1c, or Cp/G. A lower basal Cp/G is associated to lower rates of optimal glucose control after 6 months of treatment with GLP1 agonists.
Disclosure
Grants from e-DM3 to Fundación SEEN.

DOI: 10.1530/endoabs.37.EP455

EP456

Study of irisin hormone level in type 2 diabetic patients with and without diabetic neuropathy

Mohammad Halawa[1], Manal Abushady[1], Mohammed Abd El Fattah[2] & Mohammed Hassan[2]
[1]Ain Shams University, Cairo, Egypt; [2]Military Medical Academy, Cairo, Egypt.

Background and aims
Irisin is a novel myokine that promote energy expenditure. It could act on adipocyte metabolism through a novel neural pathway and on the other hand irisin induces neural proliferation and adequate neural differentiation. We aimed to assess serum irisin level in type 2 diabetics (T2DM) and correlate it with metabolic parameters. Also, we assessed the relation between irisin level and diabetic peripheral neuropathy (DPN).
Methods
We recruited 60 T2DM subjects and 30 healthy controls. Diabetics will be divided into 30 patients without complications and 30 with DPN. DN4 questionnaire was used to screen for diabetic neuropathy. Serum irisin, FPG, 2 h PG, HbA1c, TG, fasting insulin, and HOMA-IR were measured.
Results
Irisin level was significantly lower in diabetics than control (40.92 ± 17.99 ng/ml vs 160.14 ± 58.67 ng/ml, $P < 0.01$). Diabetics with PN had lower irisin than diabetics without complications (27.57 ± 7.61 ng/ml vs 54.27 ± 15.24 ng/ml, $P < 0.01$). Irisin levels were negatively correlated with FBS ($r = -0.487$), 2 h PG ($r = -0.570$), HbA1c ($r = -0.596$), fasting insulin ($r = -0.368$), HOMA-IR ($r = -0.441$), and TGs ($r = -0.327$) in all studied groups ($P < 0.01$). Also, it was negatively correlated with the duration of diabetes in all diabetics (-0.764, $P < 0.01$). We found a negative correlation between irisin and age only in healthy subjects (-0.480, $P < 0.01$). Multiple regression analysis revealed that HbA1c, age, F. Insulin, BMI, and HOMA-IR respectively were independent determinants for irisin level.
Conclusion
We found that serum irisin levels were decreased in T2DM. Lower irisin level may be associated with peripheral neuropathy. Irisin levels associated inversely with insulin resistance.

DOI: 10.1530/endoabs.37.EP456

EP457

Clinical experience with lixisenatide in patients with obesity and type 2 diabetes

Cristina Tejera[1], Esther Delgado[2], Cristina Porca[1], Francisco Morales[2], Diego Bellido[1] & José Díaz[2]
[1]Endocrinology and Nutrition Unit, University Hospital of Ferrol, Ferrol (Galicia), Spain; [2]Endocrinology and Nutrition, University Hospital of Badajoz, Badajoz (Extremadura), Spain.

Introduction
Agonist receptor-GLP1 (AR-GLP1) had demonstrated its utility in obese patients with diabetes type 2. Since August 2013 we have available in Spain a new AR-GLP1 with prandial action in a single daily dose, lixisenatide. There are different clinical trials that support its efficacy and security but the dates from real clinical practice are scarce.
Aim
To analyse the efficacy and security in real clinical practice for the treatment of diabetic type 2 patients with BMI ≥ 30 kg/m^2 in a 12 months period.
Materials and methods
Data from patients attending in an Endocrinology Unit from two Spanish centres were collected in a retrospective way ($n = 77$). Initially, during 7 days patients received lixisenatide 10 μg in single dose and later, they received the maintenance dose of lixisenatide 20 μg. Primary endpoint was change in HbA1c from baseline.

Body weight, adverse effects and others treatment for diabetes were collected. Available data were analysed with SPSS 20.
Results
77 obese (32 males, age 58.02 ± 12.5 years old) and type 2 diabetic patients (mean weight 94.53 kg, mean duration of diabetes 7.1 years, and mean HbA1c 9.01%). Data at 12 months of treatment were analysed. In this period, the HbA1c decreased −1.04 ± 0.29% ($P<0.001$) and the body weight decreased 6.26 ± 2.56 kg ($P=0.01$). Insulin was discontinued in 12.5% of the patients, mean initial dose 44 UI, mean final dose 29 UI, $P=0.01$. Mild transient gastrointestinal side effects were experimented by 8%. Three patients discontinued treatment (vomiting and refusing s.c. injection).
Conclusions
In our study, the efficacy of lixisenatide had been superior that reported in clinical trials in both aspects, HbA1c control and weight lost. In addition, this treatment had reduced the insulin requirements. Side effects are infrequent and mostly mild. More studies are necessary to support our results.

DOI: 10.1530/endoabs.37.EP457

EP458

Controlled attenuation parameter have close relationship with the prevalence and the severity of non-alcoholic fatty liver disease in a type 2 diabetes mellitus population

Jaehyuk Lee[1], Kwang Joon Kim[2], Bong Soo Cha[2] & Eun Seok Kang[2]
[1]Division of Endocrinology, Department of Internal Medicine, Myongji Hospital, Goyang-si, Republic of Korea; [2]Division of Endocrinology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea.

Background
The severity of non-alcoholic fatty liver disease (NAFLD) in type 2 diabetes mellitus (T2DM) population compared with that in normal glucose tolerance (NGT) individuals has not yet been assessed by a quantitative method. We investigated the prevalence and the severity of NAFLD in a T2DM population using controlled attenuation parameter (CAP).
Methods
Subjects who underwent testing for biomarkers related to T2DMand CAP using Fibroscan during a regular health check-up were enrolled. CAP values of 250 and 300 dB/m were selected as the cutoffs for the presence of NAFLD and for moderate to severe NAFLD respectively. Biomarkers related to T2DM included fasting glucose/insulin, C-peptide, HbA1c, glycoalbumin, and HOMA-IR.
Results
Among 340 study participants (T2DM, $n=66$; pre-diabetes, $n=202$; and NGT, $n=72$), the proportion of subjects with NAFLD increased according to the glucose tolerance status (31.9% in NGT; 47.0% in pre-diabetes; and 57.6% in T2DM). The median CAP value was significantly higher in subjects with T2DM (265 dB/m) than in those with pre-diabetes (245 dB/m) or NGT (231 dB/m) (all $P<0.05$). Logistic regression analysis showed that subjects with moderate to severe NAFLD had a 2.4-fold (odds ratio) higher risk of having T2DM than those without NAFLD ($P=0.02$; 95% CI 1.13–4.86), and positive correlations between the CAP value and HOMA-IR ($\rho=0.407$) or C-peptide ($\rho=0.402$) were demonstrated.
Conclusion
Subjects with T2DM had a higher prevalence of severe NAFLD than those with NGT. Increased hepatic steatosis was independently associated with the presence of T2DM, and insulin resistance induced by hepatic fat may be an important mechanistic connection.

DOI: 10.1530/endoabs.37.EP458

EP459

Risk factors, aetiology, and prognosis in patients with ischaemic stroke and diabetes mellitus

Julia Silva-Fernández[1], Rafael García-Ruiz[2], Paloma Moreno-Moreno[3], Rosa M García-Ruiz[4] & Carolina González-Pereira[5]
[1]Endocrinolgy Unit, Mancha Centro General Hospital, Alcázar de San Juan, Ciudad Real, Spain; [2]Neurology Unit, Mancha Centro General Hospital, Alcázar de San Juan, Ciudad Real, Spain; [3]Endocrinology Unit, Reina Sofia University Hospital, Córdoba, Spain; [4]Pedreguer Primary Care Center, Pedreguer, Alicante, Spain; [5]Intensive Care Unit, University Central Hospital of Asturias, Oviedo, Asturias, Spain.

Objective
To describe the clinical, aetiological and prognostic differences in diabetic and non-diabetic ischaemic stroke (IS) patients.
Materials and methods
Retrospective analysis of prospective series of IS patients. Patients were classified as non-DM and DM patients. Demographic and clinical characteristics were compared between two groups. IS prognosis was evaluated by modified Rankin scale (mRS) and NIHSS (NIH stroke scale).
Results
138 were included (53 diabetic and 71 non-diabetic). Mean age was 73.95 (± 14.43) years in DM patients and 74 (±11.51) in non-DM. The prevalence of hypertension (88.6% vs 66.9%, $P<0.05$), hypercholesterolemia (56.6% vs 33.8%, $P<0.05$), coronary artery disease (15% vs 8.4%, P 0.18), peripheral artery disease (3.7% vs 2.8%, P 0.76), previous stroke (33.9% vs 15.4%, $P<0.05$), and atrial fibrillation (16.9% vs 9.8%, P 0.24) was higher in DM patients compared to non-DM patients. Smoking habit was more common among non-DM patients (15.4% vs 7.5%, P 0.13). Stroke subtype distribution didn't differ between two groups: Atherothrombotic etiology (18.8% in DM patients vs 14% in non-DM patients), cardioembolic (24.5% vs 28.1%), lacunar (20.7% vs 18.3%), and undetermined (35% vs 39.4%). The prevalence of transient ischaemic attack was higher among non-DM patients (33.8% vs 22.6%, P 0.19). There were no differences in stroke severity between DM patients and non-DM patients. mRS 0–2 at discharge prevalence was 74.5% vs 76%, P 0.94. NIHSS ≥8 was 25% vs 21.1%, P 0.49 respectively.
Conclusions
Our study reveals a higher prevalence of other vascular risk factors in diabetes patients. We have found no differences in relation to IS subtype and IS prognosis.

DOI: 10.1530/endoabs.37.EP459

EP460

Establishing the relationship between third-trimester foetal abdominal circumference, birthweight, and neonatal morbidity in gestational diabetes

Maria Teresa Pereira[1], Susana Garrido[1], Raquel Almeida[1], Joana Vilaverde[1], Fernando Pichel[2], Clara Pinto[3], Joaquim Gonçalves[3] & Jorge Dores[1]
[1]Division of Endocrinology, Diabetes and Metabolism, Centro Hospitalar do Porto, Porto, Portugal; [2]Division of Nutrition, Centro Hospitalar do Porto, Porto, Portugal; [3]Division of Obstetrics, Centro Hospitalar do Porto, Porto, Portugal.

Introduction
Gestational diabetes (GD) is associated with a significantly higher risk of perinatal complications. It has been suggested that third-trimester (3thT) foetal abdominal circumference ($_f$AC) determination is an important predictor of macrossomia and large for gestational age (LGA).
Aims
The purpose of this study was to evaluate the association between the 3thT $_f$AC percentile with birthweight (BW) and adverse neonatal outcomes in a cohort of women with GD.
Methods
We retrospectively analysed the $_f$AC percentile of the 3thT ultrasound screening in pregnant women with GD within a 2 years period in a Central University Hospital. We enrolled 268 pregnant women with singleton pregnancy undergoing routine fetal biometry after 28 weeks. The relationship between $_f$AC and BW was explored using the Spearman's correlation and among $_f$AC percentile groups (<50; ≥50) and adverse neonatal outcomes using the Fisher's exact test.
Results
The study included 268 singleton pregnancies; the median maternal age was 33 years old (range, 17–52) with a median delivery week of 39 weeks (range, 29–41). The median BW was 3165 g (range, 1370–4450), 3thT ultrasound gestational age measurement 36 weeks (range, 29–40) and $_f$AC percentile 50 (range, 1–100). Neonatal outcomes prevalences: neonatal morbidity compositum ($n=67$; 25%), small for gestational age ($n=25$; 9.3%), LGA ($n=24$; 9.0%), macrossomia ($n=12$; 4.5%), and neonatal hypoglycaemia ($n=5$; 1.9%). The macrossomia and LGA rates were greater in the $_f$AC percentile group ≥50 compared to <50 (91.7% vs 8.3% and 95.8 vs 4.2% respectively) ($P<0.05$). There was no significant difference in neonatal hypoglycaemia rate between groups (80% vs 20%, $P=0.384$). We documented a strong positive correlation between $_f$AC and BW: $R=+0.626$, $P<0.001$ ($R^2=0.392$).
Conclusions
The intrapartum $_f$AC measurement was useful in screening fetal macrossomia and LGA. These results suggest that $_f$AC measured by ultrasound can help to predict the BW and seems to be a valuable parameter to be included when we evaluate a gestational diabetic pregnant woman.

DOI: 10.1530/endoabs.37.EP460

EP461

Usefulness of carotid ultrasonography as a screening test for coronary artery disease in Korean diabetic patients

In-Jin Cho[1], Sei Hyun Baik[2], Yoo-Chul Hwang[1], Kyu Jeung Ahn[1], Ho-Yeon Chung[1] & In-Kyung Jeong[1]
[1]Department of Endocrinology and Metabolism, Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea; [2]Department of Endocrinology and Metabolism, Korea University Guro Hospital, Seoul, Republic of Korea.

Carotid intima–media thickness (IMT) has been shown an independent predictive marker of coronary artery disease (CAD) and cardiovascular disease in many studies. We investigated the usefulness of carotid IMT as a screening test for CAD in Korean diabetic patients. We conducted retrospective study and found the type 2 diabetic patients without cardiovascular disease history who underwent carotid ultrasonography (US) and stress echocardiography (SE) from June 2006 to December 2012 at Kyung Hee University Hospital at Gangdong. Total 218 patients were reviewed by medical record, laboratory data, carotid US, SE, and coronary angiography results. Carotid US abnormalities were defined as $\geq$1 mm IMT or detection of plaque. Significant CAD was defined as $\geq$50% luminal narrowing in $\geq$1 epicardial arteries or their major branches. We assessed predictive value for CAD according to results of carotid US or SE.
116 patients (53.2% of 218 patients) had carotid US abnormalities and 34 patients (15.6% of 218 patients) shown positive SE. Patients with carotid plaque were old age (65.4$\pm$9.5 years vs 56.7$\pm$9.3 years, $P<0.001$), had long duration of diabetes (11.8 years vs 7.8 years, $P<0.001$), and low BMI (25.1$\pm$3.4 kg/m^2 vs 26.4$\pm$3.6 kg/m^2, $P<0.001$) compared to patients with normal carotid US. However, there was no difference in prevalence of positive SE between patients with carotid plaque and patients with normal carotid US (15.5% vs 15.7%, $P=0.968$). In patients with positive SE, there was no difference in prevalence of significant CAD whether they had carotid plaque or not.
52 of 218 patients underwent coronary angiography. 32 of 52 patients had positive SE and positive predictive value of SE in significant CAD was 84.4% (27 of 32 patients). Of 32 patients with positive SE, 16 patients had carotid plaque and all of them had significant CAD. In conclusion, carotid US abnormalities alone had limitation to correlated SE results and predict significant CAD. However, when taking into carotid US results with SE results, they improved positive predictive value in significant CAD.

DOI: 10.1530/endoabs.37.EP461

EP462

Beneficial effects of antioxidant property of *Aegle marmelos* leaves serum antioxidant status on blood glucose levels in diabetes type 2 subjects

Vinita Nigam & Vanisha Nambiar
MS University, Vadodara, Gujarat, India.

Background
Diabetes mellitus is one of the most recognized and clinically significant disorders of the endocrine system, Based on recent advances and involvement of oxidative stress in complicating diabetes mellitus, efforts are on to find suitable antidiabetic and antioxidant therapy. *Aegle marmelos* (L.) Corr. is one of the most important Indian medicinal plants which has enormous traditional values against various diseases and many bioactive compounds have been isolated from this plant.
Methods
In the present study 60 NIDDM patients on oral hypoglycaemic drugs were randomly divided into two groups; 30 subjects (11 males and 19 females) were supplemented with the juice of *A. marmelos* fresh leaves (20 g/100 ml) every morning empty stomach for 60 days against 30 (14 males and 16 females) subjects as controls. The 'antioxidant power' of the serum (ferric reducing ability of plasma), was taken as the indicator of total antioxidant potential.
Results
Supplementation of the juice significantly ($P<0.0001$) decreased fasting blood glucose and HbA1c levels and significant ($P<0.0001$) increase in serum antioxidant activity (serum FRAP). Whereas significant ($P=0.008$) increase in fasting blood glucose levels and significant decrease in serum antioxidant activity ($P<0.0001$) was observed for control.
Conclusion
The present study proves the antidiabetic activity of the *A. marmelos* leaves. We believe antioxidant therapy along with monitoring of host antioxidant defence would definitely help in blocking the effects of oxidative stress. We propose that *A. marmelos* leaf juice as an antioxidant therapy monitored with the help of FRAP assay along with oral hypoglycaemic drugs can control blood glucose to normal levels in patients whose diabetes is not controlled with these agents or produce adverse effects on dose increments.
Disclosure
UGC BSR.

DOI: 10.1530/endoabs.37.EP462

EP463

Male patients benefit from initial exenatide treatment: a real-world experience

Liang Chen, Jian Kuang, Jianhao Pei, Hongmei Chen, Zhong Chen, Zhongwen Li, Huazhang Yang, Xiaoyin Fu, Long Wang & Zhijiang Chen
The First Division of Endocrinology, Guangdong Academy of Medical Sciences, Guangdong General Hospital, Guangzhou City, China.

Objective
The purpose of this study was to describe the outcome after initiation of exenatide therapy and to determine whether the impact of adverse drug reactions on compliance was affected by gender.
Methods
A retrospective study was performed of 18 diabetic patients (eight males) that were prescribed exenatide between June 2013 and September 2014. Each included patient received exenatide for $\geq$1 month. Age, disease course, race, BMI, medical history, chronic complications associated with diabetes, and the state of pretreatment glycaemic control were analyzed. Both 1 and 4 weeks after treatment, data such as blood glucose, blood lipids, and body weight were collected to determine any adverse drug reactions and the impact of gender on exenatide withdrawal.
Results
The incidence of adverse drug reaction was significantly higher in female than male patients following exenatide treatment ($P<0.05$). Although there was no significant difference between the male and female group 1 week, adverse drug reactions continued longer in females and the incidence of adverse drug reaction was significantly higher in female patients 4 weeks after initiating treatment ($P<0.01$). As a result, four female patients stopped taking the medication, whereas only one male patient stopped taking the medication because the patient was unaccustomed to the drug injection process. The efficacy of exenatide was similar between the two groups at both 1 and 4 weeks.
Conclusion
Exenatide, a glucagon-like peptide 1 agonist often causes relatively significant gastrointestinal reactions during its initial application. Gender difference in adverse drug reactions may be due to the impact of this drug on the feeding centre in the CNS.

DOI: 10.1530/endoabs.37.EP463

EP464

Occurrence frequency of diabetic foot syndrome in three pilot regions of Uzbekistan

Nilufar Ibragimova[2], Telman Kamalov[1], Khamidulla Shokirov[1], Lyudmila Kokareva[1] & Oxana Platonova[2]
[1]Republican Research and Practical Medical Centre of Endocrinology, Tashkent, Uzbekistan; [2]Public Association of the Disabled and People with Diabetes Mellitus 'UMID', Tashkent, Uzbekistan.

Goal
To study occurrence frequency of diabetic foot syndrome (DFS) in three pilot regions of Uzbekistan.
Material and methods
Upon WDF project, 'UMID' Association of Tashkent and RRPMCE have screened T1DM and T2DM patients for DFS in three pilot regions (Andizhan, Tashkent, and Kashkadarya areas). 663 patients examined; of them 581 T2DM patients and 82 T1DM peoples in the 25–65 age groups with duration of the disease 5–15 years. Results of USI Doppler velocimetry, levels of glycaemia, HbA1c, cholesterol, HDL, LDL, and triglycerides were studied.
Results
83.2% of T2DM and 67.4% of T1DM had diabetic polyneuropathy. Frequency of DFS occurrence was 55.3% (T2DM) and 31.7% (T1DM) accordingly. The greatest number of lower limb amputations (3.8%) and re-amputations (2.0%) was found in T2DM patients with disease of 7–10 years. Results of interviews

pertaining to rules of foot care showed a poor knowledge on DFS prevention which explains a rise in a number of amputations in PDM in rural regions. 94.2% of PDM were in a decompensation stage (HbA1c $>9.5\%$) irrespective of history of the disease. 68% of PDM were hypertensive. 36% of PDM (mostly T2DM patients with obesity grades 1 and 2) had high levels of cholesterol and LDL (5.6 ± 0.7 and 4.01 ± 0.12 mmol/l respectively) with low level of HDL (0.53 ± 0.05 mmol/l) and level of triglycerides of 2.8 ± 0.3 mmol/l.

Conclusions

i) Frequency of DFS occurrence in three pilot regions of Uzbekistan made 55.3% in T2DM patients and 31.7% in those of T1DM; ii) the greatest number of lower limb amputations (3.8%) and re-amputations (2.0%) was found in T2DM patients with duration of the disease 7–10 years; and iii) decompensation stage (HbA1c $>$ 9.5%) in 94.2% of PDM is one of principal causes of high frequency of DFS occurrence and a considerable number of amputations in PDM.

Disclosure

World Diabetes Foundation grant number 08-379, dd 07.09.2009.

DOI: 10.1530/endoabs.37.EP464

EP465

Nocturnal blood pressure is related to the progression of retinopathy in type 1 diabetic patients

Francisco Javier Vílchez-López[1], Isabel Mateo-Gavira[1], Laura Larrán-Escandón[1], Ana Montero-Galván[1], José Ortego-Rojo[1], María Victoria García-Palacios[2] & Manuel Aguilar-Diosdado[1]

[1]Endocrinology, Puerta del Mar Hospital, Cádiz, Spain; [2]Preventive Medicine and Public Health, Cádiz, Spain.

Introduction

The objective is to evaluate the relationship between early blood pressure alterations (detected by ambulatory blood pressure monitoring (abpm)) and the development/progression of retinopathy in patients with type 1 diabetes clinically normotensive.

Methods

We designed a prospective observational study of 85 patients, clinically normotensive and without microalbuminuria, monitored over 7 years. Abpm was performed over 24 h and subclinical hypertension was considered if: i) mean systolic pressure (sbp) was >130 mmHg in the 24 h and daytime periods and >120 mmHg in the nighttime period and/or mean diastolic pressure (dbp) >80 or 70 mmHg in the same periods respectively and/or ii) more than 50% of the readings were higher than the defined previous criteria. Non dipper pattern was defined as nocturnal sbp or dbp $<10\%$ relative to the diurnal mean value. We evaluated the development or progression of retinopathy during the following period.

Results

Of the 85 patients included in the analysis, 55.3% (*n*: 47) were women with an average age of 27.9 ± 6.1 years and a length of disease of 12.3 ± 6.5 years. 23.5% were diagnosed with subclinical hypertension and 36% with non-dipper pattern as the only pathological finding. 69 patients completed the seven-year follow-up. During this period, 31.8% presented development or progression of retinopathy. Initial mean nocturnal dbp (OR: 1.122, *P*: 0.034), waist perimeter (OR: 1.075, *P*: 0.028), and final non-dipper pattern (OR: 5.857, *P*: 0.005) showed as independent risk factors of progression/development of retinopathy.

Conclusions

In type 1 diabetic patients clinically normotensive there is a high prevalence of blood pressure alterations detected by abpm. Nocturnal blood pressure parameters predisposes the development or progression of retinopathy.

DOI: 10.1530/endoabs.37.EP465

EP466

Nocturnal blood pressure is related to the development of microalbuminuria and established hypertension in patients with type 1 diabetes

Francisco Javier Vílchez-López[1], Isabel Mateo-Gavira[1], Laura Larrán-Escandón[1], Ana Montero-Galván[1], José Ortego-Rojo[1], María Victoria García-Palacios[2] & Manuel Aguilar-Diosdado[1]

[1]Endocrinology, Puerta del Mar Hospital, Cádiz, Spain; [2]Preventive Medicine and Public Health, Puerta del Mar Hospital, Cádiz, Spain.

Introduction

The objective is to evaluate the relationship between early blood pressure alterations (detected by ambulatory blood pressure monitoring (abpm)) and the development of microalbuminuria and arterial hypertension in patients with type 1 diabetes clinically normotensive.

Methods

We designed a prospective observational study of 85 patients, clinically normotensive and without microalbuminuria, monitored over 7 years. Abpm was performed over 24 h and subclinical hypertension was considered if: i) mean systolic pressure (sbp) was >130 mmHg in the 24 h and daytime periods and >120 mmHg in the nighttime period and/or mean diastolic pressure (dbp) >80 or 70 mmHg in the same periods respectively and/or ii) more than 50% of the readings were higher than the defined previous criteria. Non-dipper pattern was defined as nocturnal sbp or dbp $<10\%$ relative to the diurnal mean value. We evaluated the development of microalbuminuria and established hypertension during the following period.

Results

Of the 85 patients included in the analysis, 55.3% (*n*: 47) were women with an average age of 27.9 ± 6.1 years and a length of disease of 12.3 ± 6.5 years. 23.5% were diagnosed with subclinical hypertension and 36% with non-dipper pattern as the only pathological finding. 69 patients completed the 7-year study. During this period: i) 10.14% developed microalbuminuria, showing the mean nocturnal sbp as a risk factor (OR: 1.129, *P*: 0.007) and ii) 7.24% of the normotensive patients progressed to established hypertension, showing historical HbA1c (OR: 2.767, *P*: 0.046) and mean nocturnal dbp (OR: 1.243, *P*: 0.046) as related factors.

Conclusions

In type 1 diabetic patients clinically normotensive with normoalbuminuria, nocturnal blood pressure parameters predisposes the development of micro-albuminuria and established hypertension.

DOI: 10.1530/endoabs.37.EP466

EP467

Subclinical blood pressure alterations are related to proinflammatory markers in type 1 diabetes mellitus

Francisco Javier Vílchez-López[1], Isabel Mateo-Gavira[1], Ana Montero-Galván[1], Francisco Visiedo-García[2], María Victoria García-Palacios[3], Laura Larrán-Escandón[1] & Manuel Aguilar-Diosdado[1]

[1]Endocrinology, Puerta del Mar Hospital, Cádiz, Spain; [2]Investigation Unit, Hospital Puerta del Mar, Cádiz, Spain; [3]Preventive Medicine and Public Health, Puerta del Mar Hospital, Cádiz, Spain.

Introduction

The objective is to evaluate the relationship between precocious subclinical hypertension and inflammatory and endothelial dysfunction markers in normotensive and normoalbuminuric patients with type 1 diabetes.

Methods

We designed an observational transversal study of 85 patients, clinically normotensive and without microalbuminuria. Ambulatory blood pressure monitoring (abpm) was performed over 24 h and subclinical hypertension was considered if: i) mean systolic pressure (sbp) was >130 mmHg in the 24 h and daytime periods and >120 mmHg in the nighttime period and/or mean diastolic pressure (dbp) >80 or 70 mmHg in the same periods respectively and/or ii) more than 50% of the readings were higher than the defined previous criteria. Non dipper pattern was defined as nocturnal sbp or dbp $<10\%$ relative to the diurnal mean value. We analyzed the relationship between the blood pressure alterations detected by abpm and inflammatory cytokines (IL6, TNFα, and VEGF) and markers of endothelial damage (VCAM, ICAM, and PAI).

Results

Of the 85 patients included in the analysis, 55.3% (*n*: 47) were women with an average age of 27.9 ± 6.1 years and a length of disease of 12.3 ± 6.5 years. 31.8% presented pathological mean blood pressure parameters in some of the periods. VEGF levels were significantly higher in patients with diurnal blood pressure alterations relative to normotensive patients (112.33 (72.87–213.53) pg/ml vs 71.03 (37.71–107.92) pg/ml; $P=0.007$). In addition, VEGF levels showed a significant correlation with mean daytime and 24 h blood pressure parameters. IL6 levels showed as a risk factor in patients diagnosed with subclinical hypertension (OR: 1.406, *P*: 0.027). There were no modifications in the level of markers of endothelial damage.

Conclusions

An increase in proinflammatory cytokines, although not markers of endothelial damage, exists in precocious stages of hypertension in type 1 diabetic patients.

DOI: 10.1530/endoabs.37.EP467

EP468

Different stress hormone response in insulin pump treatment compared with multiple daily injection: preliminary data

Antonio Mancini, Jacopo Pareo, Chantal Di Segni, Sebastiano Raimondo, Alessandro Rizzi & Dario Pitocco
Department of Medical Sciences, Catholic University of Sacred Heart, Rome, Italy.

It is known that in type 1 diabetes mellitus (T1DM) continuous subcutaneous insulin infusion (CSII) therapy improves metabolic control and reduces risk of hypoglycaemia in comparison with multiple daily injection (MDI). Metabolic outcomes usually considered are HbA1c, BMI, and inflammatory parameters. However few data are available on pituitary and gonadal hormone responses, which are involved in metabolic processes. In order to study the response of anabolic hormones in patients treated with CSII or MDI, we have evaluated IGF1, DHEAS, and testosterone levels in a cohort of T1DM patients, comparing these two different ways of intensive insulin administration. We enrolled 41 patients, aged 19–55 years, 25 males and 16 females; 23 were treated by MDI (group 1) and 18 by CSII (group 2). The groups were similar for age, BMI, and duration of DM. IGF1 was assayed using the electro-chemiluminescent immunoassay (ECLIA) method instead testosterone and DHEAS using the chemiluminescent microparticle immunoassay (CMIA) method. Despite similar glycaemic control (mean ± s.d., HbA1c: 8 ± 0.01 in males and 7 ± 0.01 in females of group 1; 7 ± 0.01 both in males and females of group 2), we found in males a significant difference in IGF1 levels (138.8 ± 9.4 in group 1 and 96.2 ± 11.2 ng/ml in group 2, $P<0.05$) and a not significant trend toward higher DHEAS levels (2912 ± 432.9 and 1909.6 ± 216.9 ng/ml); T levels were higher in females of group 1 than group 2 (1.2 ± 0.8 and 0.5 ± 0.1 ng/ml).
These preliminary data seem to indicate a different hormone response in patients treated by CSII or MDI, with lower stress hormone pattern response for patients on CSII, despite similar glycaemic control. Better ovarian response was observed in women on CSII, with lower androgen production. Further studies are needed to better understand these complex relationships and their prognostic implications.

DOI: 10.1530/endoabs.37.EP468

EP469

Evaluating analogue vs human insulin efficacy in real life: observational study in type 2 Albanian diabetic patients, previously insulin treated

Florian Toti[1,2], Gjinal Gjonçaj[1], Blerina Resulaj[2], Luftime Bruka[1], Adriana Lapardhaja[1], Manjola Carçani[1], Rajmonda Tare[1] & Varvara Lile[1]
[1]University Hospital Center 'Mother Theresa', Tirana, Albania; [2]Faculty of Medicine, Tirana, Albania.

Background and aims
Insulin therapy is an important part of diabetes treatment. A lot of studies have compared the efficacy of new insulin therapies, but in our country, specialists still have to demonstrate at the institutions the treatment's efficacy and cost-effectiveness for new insulin analogues. The aims of our study is to evaluate the efficacy of analogues vs human insulins and differences between various analogue insulin, in type 2 diabetes patients, previously treated with human insulin.
Methods
This study is realised in real life patients. We retrospectively included 384 patients, previously treated ≥24 months with human insulins, switched to an analogue insulin for ≥12 months. Treatment efficacy was evaluated by HbA1c levels, weight difference and changes in total daily dose (TDD) analogue vs human.
Results
384 patients, 185 (48.17%) males. Glargine 194 (50.5%), detemir 110 (28.65%), and all other analogs (AOA) 80 (20.85%). Mean age 62.19 (s.d. 10.12) years, mean diabetes duration 10.8 (s.d. 5.35) years. Mean duration on analogue insulin therapy was 19.1 months. Overall mean HbA1c was 8.86 (s.d. 1.06) vs 7.51 (s.d. 1.51) on analogues $P<0.01$. TDD was 54.9 UI (s.d. 20.1) vs 62.56 UI (s.d. 27.95) on analogues $P<0.05$, but smaller basal doses 29.28 UI vs 28.1 UI. 21% of the patients on human insulin had an HbA1c <7% vs 63.1% on analogues. Patients on analogues had a slight weight increase +3.18 kg during the study period (P 0.55), but DE/GL 1.48 kg vs 4.14 kg ($P<0.01$).
Conclusions
A better metabolic control was noted with analogue vs human insulins, with smaller daily doses of basal insulin and minimal weight increase. Even in our study detemir group had a smaller weight gain, making it preferable for obese type 2 diabetics.

DOI: 10.1530/endoabs.37.EP469

EP470

Telemedicine as a motivational tool to optimise metabolic control in patients with diabetes in Turkey: results from a randomised controlled trial

Ilhan Satman[1], Elif Bagdemir[1], Fulya Turker[1], Selda Celik[1], Cemile Idiz[1] & Haluk Ozsari[2]
[1]Division of Endocrinology and Metabolism, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey; [2]Faculty of Health Science, Istanbul University, Istanbul, Turkey.

Objective
Our purpose was to evaluate the impact of a transmission system on metabolic control of patients with diabetes.
Research design and methods
This ongoing-prospective, randomized, comparative study included adult patients with type 1 ($n=71$) and type 2 diabetes ($n=139$). Consecutive patients were equally allocated into two groups. Both groups received routine care by the same health care professionals (HCPs) 3-monthly. TeleDiab group additionally transmissed SMBG data and received feedbacks and SMSs regularly.
Results
We reviewed metabolic parameters based on mean difference from baseline to 9 months. In TeleDiab group, fasting blood glucose (FBG: −19 mg/dl, $P=0.089$), HbA1c (0.6%, $P<0.001$), HDL-cholesterol (−3.6 mg/dl, $P=0.006$), systolic (SBP: −5.3 mmHg, $P=0.001$), and diastolic blood pressures (DBP: −2.7 mmHg, $P=0.055$) remarkably reduced from baseline. While in control group HbA1c (−0.4%, $P=0.004$) only reduced but BMI (0.6 kg/m^2, $P=0.014$) increased significantly; additionally, SBP (−2.8 mmHg, $P=0.099$) and DBP (−2.4 mmHg, $P=0.079$) tended to decrease tended to increase from baseline.
In TeleDiab group, we observed positive correlations between average number of SMBG and change from baseline to 9 months FBG (monthly post-prandial: $r=0.256$, $P=0.029$) and weight (daily post-prandial: $r=0.229$, $P=0.049$); and negative correlations between average number of SMBG and change from baseline to 9 months HDL-cholesterol (daily postprandial: $r=-0.261$, $P=0.026$), SBP (weekly total: $r=-0.276$, $P=0.017$; weekly pre-prandial: $r=-0.233$, $P=0.046$; monthly total: $r=-0.272$, $P=0.019$; monthly pre-prandial: $r=-0.247$, $P=0.034$; and monthly post-prandial: $r=-0.247$, $P=0.035$), and DBP (weekly post-prandial: $r=-0.284$, $P=0.044$; monthly total: $r=-0.234$, $P=0.044$; and monthly post-prandial: $r=-0.316$, $P=0.006$).
At 9-month, more patients with type 2 diabetes in TeleDiab group achieved optimal HbA1c as compared with control group (52.1% vs 38.3%, $P=0.061$).
Conclusion
Regular follow-up visits by the same HCPs resulted with improved glycaemic, lipid and BP control in subjects with diabetes. However, further improvement was achieved with the use of electronic transmission system.
Disclosure
This work is partly supported by Turkcell Telecommunication Company (2904/2012).

DOI: 10.1530/endoabs.37.EP470

EP471

Long-term tele-monitoring of patients with type 2 diabetes mellitus: ancillary analysis of the results of the Greek pilot of the renewing health multicentre randomised control trial

George E Dafoulas[1,2], Afentoula Mavrodi[3], Charalampos Giannakakos[4], Paraskevi Gkiata[5], Kyriaki Theodorou[1], Vasilios Aletras[3], Panagiotis Stafylas[6], Georgios Koukoulis[1,7] & Alexandra Bargiota[1,7]
[1]Faculty of Medicine, University of Thessaly, Larisa, Greece; [2]E-Trikala Telehealth Center, Municipality of Trikala, Trikala, Greece; [3]Department of Business Administration, University of Macedonia, Thessaloniki, Greece; [4]5th Regional Health Authority of Thessaly and Sterea, Larisa, Greece; [5]Telehealth Center, Intermunicipal Digital Community of Central Greece, Trikala, Greece; [6]Health Information Management, Brussels, Belgium; [7]Department of Endocrinology and Metabolic Diseases, Regional University Hospital, Larisa, Greece.

Introduction
To evaluate the impact of a long-term telemonitoring programme for patients with type 2 diabetes mellitus (DMT2) on glycaemic control and lipid disorders.
Methods/design
In the Greek pilot of a prospective, randomised, single-blinded, multicentre study 154 patients with DMT2, HbA1c >53 mmol/mol (7.0% according to NGSP) and capable of using the telemonitoring device, were studied after randomly assigned in the telemonitoring (IG) ($n=74$) and the control group (CG) ($n=80$) and after having signed the informed consent form. In the IG group patients' blood glucose

profiles were collected weekly using a mobile phone health platform, for a period of 1 year. Allocated health professionals provided via phone the appropriate counselling on lifestyle and medication changes whenever required. Patients in (CG) group received usual care with face-to-face consultations. Levels of HbA1c (primary outcome), total cholesterol (TChol), LDL, and triglycerides (Tg) were measured at the beginning and the end of the study.

Results

The table shows the outcome of the variables studied in both groups. A greater reduction in HbA1c was observed in the IG compared to the CG. Linear regression analysis performed proved that no significant contribution to the reduction of HbA1c level could be attributed to patients' demographics, age ($R^2=0.099$, $P=0.103$), gender ($R^2=0.061$, $P=0.316$), level of education ($R^2=0.034$, $P=0.572$), prior use of computer ($R^2=0.062$, $P=0.309$), and prior use of mobile phone ($R^2=0.005$, $P=0.406$).

Outcome	Mean difference between groups (95% CI)	*P* value
HbA1c (mmol/mol)	−6.13 (−10.45 to −1.81)	0.001
TChol (mg/dl)	−2.41 (−18.48 to 13.65)	0.765
LDL (mg/dl)	−6.72 (−16.02 to 2.57)	0.155
Tg (mg/dl)	−12.90 (−49.97 to 24.17)	0.490

Conclusion

In the present study home telemonitoring was proven to be more effective than usual care in improving glycaemic control.

Disclosure

RENEWING HEALTH and UNITED FOR HEALTH are partially funded under the ICT Policy Support Programme (ICT PSP) as part of the Competitiveness and Innovation Framework Programme by the European Community.

DOI: 10.1530/endoabs.37.EP471

EP472

Is diabetes an independent risk factor of perioperative complications after abdominal gynecologic interventions?

Joanna Swirska[1,2], Beata Matyjaszek-Matuszek[1], Piotr Czuczwar[3] & Agnieszka Zwolak[1,2]

[1]Department of Endocrinology, Medical University of Lublin, Lublin, Poland; [2]Chair of Internal Medicine, Department of Internal Medicine in Nursing, Medical University in Lublin, Lublin, Poland; [3]3rd Chair and Department of Gynecology, Medical University of Lublin, Lublin, Poland.

Purpose

We sought to determine if in the group of patients who underwent gynecologic abdominal interventions diabetes was an independent risk factor of perioperative complications.

Material and methods

The study group included 62 women from both the diabetic and the control group who underwent elective gynecologic laparotomies such as hysterectomy or adnexectomy. The patients from diabetic group were pair-matched with patients without diabetes based on the following criteria: similar age and BMI, the same gynecologic diagnosis, undergoing the same type of gynecologic surgery, operation being performed on in the same operating room and hospitalization within the same time interval. In every matched couple of patients (diabetic vs non-diabetic patient) we compared: number and characteristics of intra- and postoperative complications, postoperative length of stay in hospital, decrease in hemoglobin level, increase in body temperature and postoperative use of antibiotics.

Results

The study did not show any statistically significant differences between the diabetic patients and corresponding patients from the control group in terms of the examined parameters.

Conclusion

Diabetes was not an independent risk factor of early postoperative complications after abdominal adnexectomies and hysterectomies in the examined group of patients. Good pre-operative glycemic control and keeping blood glucose in intra and postoperative time within normal ranges results in the reduction of complications in diabetic patients to the level typical of non-diabetics.

DOI: 10.1530/endoabs.37.EP472

EP473

Education for diabetes self-management improves quality of life and reduces HbA1c levels in people with diabetes

Florian Toti[1], Elvisa Sokoli[2], Eliora Kulluri[2], Adriana Lapardhaja[1] & Manjola Carçani[1]

[1]University Hospital Center 'Mother Theresa', Tirana, Albania; [2]Faculty of Psychology and Social Work, Tirana, Albania.

Backgrounds and aims

Knowing about patient's quality of life (QoL) is becoming increasingly important in delivering diabetes care and education. The purpose of our study was to estimate if the diabetes education improves patient QoL and reduces HbA1c levels.

Material and methods

The study sample included diabetic patients who attended a 5-day educational sessions at the Service of Endocrinology in Tirana/Albania. Patients were evaluated regarding their QoL at baseline and 6 or 12 months after their hospitalization. The HbA1c was measured at baseline, 6 and 12 months later. The diabetes QoL (DQoL) measure was used to assess the subjective QoL. DQoL is a validated 46 items survey covering four areas of interest: satisfaction and impact of treatment, worry about the future effects of diabetes and worry about social issues, as well a single question about the general health. A satisfactory level is accepted as a transformed score >60.

Results

The group consisted of 395 patients, 139 males (35%) and 256 females, 97 (24.5%) type 1 diabetes, mean age 44.2 ± 4.7 years, diabetes duration 11.4 ± 5.4 years, treated with insulin in 45% of cases, with baseline HbA1c $9.1\pm1.67\%$, having decreased respectively $8.5\pm1.1\%$ at 6 months ($P<0.05$) and $8.02\pm1.23\%$ at 12 months after hospitalization ($P<0.001$). DQoL at baseline was 56 ± 4.5, 68.2 ± 5.7 at 6 months later and 75.1 ± 3.5 at 12 months interval ($P<0.05$). The satisfaction with treatment and worry about the future were the most improved scores at 6 and 12 months after.

Conclusions

The education for self-management of the disease improves patients' QoL as well their metabolic control.

DOI: 10.1530/endoabs.37.EP473

EP474

Prevalence of microalbuminuria and predictive factors in a group of Albanian diabetic adults

Eduard Spahiu[1], Mimoza Ismaili[1], Aldi Shehu[2], Erion Thengjilli[1], Albana Doko[1] & Florian Toti[1]

[1]University Hospital Center 'Mother Theresa', Tirana, Albania; [2]Laboratory 'Intermedica', Tirana, Albania.

Background and aims

Diabetic nephropathy is one of the most prevalent and dangerous chronic complication of diabetes mellitus. Its end-stage, renal chronic failure is the most important cause of premature death in diabetic patients. Microalbuminuria (MA), one of the first signs of diabetic nephropathy, may be present from the moment of diagnosis in type 2 diabetes. The aim of our study was to determine the prevalence of microalbuminuria and to identify predictor factors in a group of Albanian diabetic adult patients.

Material and methods

Diabetic patients selected randomly, assigned by hospital admissions in Tirana University Hospital Center, Shkodra and Pogradec regional hospitals. Biochemical examinations, anthropometric measurements, and measurement of microalbuminuria by DCA 2000 in a urine spot, was performed. Microalbuminuria was considered positive if ≥20 mg or albumine/creatinine report ≥25.

Results

321 patients participated in the study. 163 women (50.78%). The mean age 58.21 ± 11.87 years, type 1 diabetes 19 patients (8.6%), mean diabetes duration 8.19 ± 6.96, and mean HbA1c $8.2\pm2.1\%$. Prevalence of MA 40.81%, while the

overt diabetic nephropathy was present in 2.8% of cases. 9/27 patients (33.3%) with newly diagnosed diabetes presented already MA. Central obesity, presence of hypertension >140/90 mmHg, HbA1c >8%, and diabetes duration >15 years were risk factors for microalbuminuria.
Conclusions
Diabetic nephropathy is a common chronic complication of diabetes mellitus. Its early detection, and an aggressive treatment of its risk factors may prevent its progression. The search for the presence of MA might be part of the initial assessment for each person with type 2 diabetes.

DOI: 10.1530/endoabs.37.EP474

EP475

Glycaemic control and weight evolution in type 2 diabetic patients with dapagliflozina in addition to their previous treatment

Lidia Urbón López de Linares, Maria Cristina Crespo Soto, Marta Ventosa Viña, Concepción Terroba Larumbre, Claudia Martín Monclús, Tomás Martín Martín & Luis Cuellar Olmedo
Hospital Universitario Rio Hortega, Valladolid, Spain.

Introduction
From November 2013 it is available in Spain a new drug to treat type 2 diabetes (DM2): dapagliflozina. The new mechanism of action consists in the inhibition of the sodium–glucose co transporters (SLGT2) inhibiting glucose reabsorption in the proximale tubule and increasing glucose excreted in the urine. Therefore hyperglycaemia decreases and so does weight as a consequence of glycosuria. This is a very convenient side effect since DM2 is highly associated with overweight/obesity.
Methodology
This is an observational retrospective study where the results of ten patients (eight females and two males) after 3 months of treatment are shown.
Results
The average age was 58.2 (±10.5) years, nine patients had been diagnosed of obesity, average BMI was 37.1 (±8.6). The initial average HbA1c was 8.43% (±1.62) and the average weight was 94.5 (±20.9) kg, after 3 months of treatment, The average HbA1c was 7.45 (±0.86) and average weight 90.4 (±19.2) kg with a medium loss of 4.26 (0.2–14.5) kg. The uric acid levels were evaluated in eight patients. The initial average level was 5.63 (±1.46) mg/dl, and after 3 months of treatment it was 4.68 (±1.15) mg/dl. In the follow-up visit 90% of the patients were still on dapagliflozine. Three of them had a case of urinary infection, one decided to stop using the drug by herself, the other two patients were given antibiotic therapy and there was no need to stop using the drug. No other side effects were described.
Conclusions
Dapagliflozina improved the glycaemic control; all the patients experienced a loss of weight; a decrease of the uric acid serum levels was seen; the most common side effect was non-complicated urinary infection that was solved with antibiotic therapy.

DOI: 10.1530/endoabs.37.EP475

EP476

Pregnancy planning in type 1 diabetes mellitus

Paloma Moreno-Moreno, Rafael Palomares-Ortega, Ana Barrera-Martin & María Ángeles Gálvez-Moreno
Management Unit of Clinical Endocrinology and Nutrition, University Hospital Reina Sofía, Córdoba, Spain.

Objective
The aim of this study was to determine the prevalence of pregnancy planning in women with type 1 diabetes mellitus (DM1) and analysing differences associated with unplanned pregnancy.
Patients and methods
Retrospective descriptive study of pregnancies in women with DM1 (2004–2012). Variables analysed: age, time of diabetes evolution, microvascular complications, and maternal outcomes (HbA1c, preeclampsia, abortions, and Caesarean section) and neonatal outcomes (perinatal death, gestational age at delivery, birth weight, and congenital malformations). The pregnancies were divided in groups attending to pregnancy planning and were analysed to evaluate possible differences between them (group 1: planned and group 2: unplanned).
Statistical analysis
Comparing proportions with the χ^2 and comparing means with Student's *t*-test.
Results
132 pregnancies. Caucasian 99.2%. Unplanned pregnancy: 67.4%. Group 1 vs group 2: 31.84±4 years old vs 29±4.5 years old, $P=0.34$; time of diabetes evolution: 13.5±8.1 years vs 13.1±7.7 years, $P=0.56$; nonproliferative diabetic retinopathy: 4.6% vs 5.6%, $P=0.5$; proliferative diabetic retinopathy 9.3% vs 8.9%, $P=0.9$; microalbuminuria 0% vs 3.3%, $P=0.22$; nephropathy 0% vs 2.24%, $P=0.32$; hypertension 0% vs 2.24%, $P=0.32$; undertreated hypothyroidism: 23% vs 18.2%, $P=0.45$; smoking 7% vs 12.5%, $P=0.33$; HbA1c (%): before pregnancy 6.4±0.4 vs 8.04±1.3, $P=0.00$; first trimester 6.36±0.5 vs 7.6±1, $P=0.004$; second trimester 6.01±0.5 vs 6.63±1, $P=0.01$; and third trimester 6.14±6.77 vs 6.77±0.7, $P=0.21$. Maternal and neonatal outcomes (group 1 vs group 2): preeclampsia 0% vs 3.5%, $P=0.21$; abortions 6.9% vs 8.04%, $P=0.7$; Caesarean section 55% vs 44.8%, $P=0.3$; perinatal death 0% vs 1.1%, $P=0.9$; gestational age at delivery 38.5±1.8 weeks vs 37.8±2.4 weeks, $P=0.1$; macrosomia 25.6% vs 35%, $P=0.28$; neonatal hypoglycaemia 5% vs 5.3%, $P=0.9$; and congenital malformations 7.2% vs 7.3%, $P=0.9$.
Conclusions
Gestation planning is deficient and is associated with glycaemic control deficit at the beginning of gestation. Glycaemic control is similar in third trimester of pregnancy, and maternal and neonatal outcomes were similar in both groups.

DOI: 10.1530/endoabs.37.EP476

EP477

Web-based telemedicine system is useful for monitoring glucose control in pregnant women with diabetes

María del Carmen Ayala Ortega[1], Florentino Carral San Laureano[1], Carmen González Macías[2], Ana Isabel Jiménez Millán[1], Juan Jesus Fernandez Alba[2], Antonia Piñero Zaldivar[1] & Concepción García Calzado[1]
[1]Endocrinology Department, Puerto Real University Hospital, Puerto Real, Cádiz, Spain; [2]Obstetric and Gynecology Department, Puerto Real University Hospital, Puerto Real, Cádiz, Spain.

Objective
The aim of this study was to examine the impact of a web-based telemedicine system for monitoring glucose control in pregnant women with diabetes on health care visits, metabolic control and pregnancy outcomes.
Subjects and methods
A prospective, single-centre, and interventional study with two parallel groups was performed in Puerto Real University Hospital (Spain). Women were assigned to two different glucose monitoring groups: control group (CG) that was managed only by follow-up with the Gestational Diabetes Unit (GDU) and telemedicine group (TMG) that was monitored both by more spaced GDU visits and a web-based telemedicine system. The number of health care visits, degree of metabolic control and maternal and neonatal outcomes were evaluated.
Results
104 pregnant women with diabetes (77 with gestational diabetes, 16 with type 1 diabetes, and 11 with type 2 diabetes) were included in the TMG ($n=40$) or in the CG ($n=64$). There were no significant differences in mean HbA1c level during pregnancy or after delivery, despite significantly lower number of visits to the GDU (3.2±2.3 vs 5.9±2.3 visits, $P<0.001$), nurse educator (1.7±1.3 vs 3.0±1.7 visits, $P<0.001$), and general practitioner (3.7±2.0 vs 4.9±2.8 visits, $P<0.034$) in the TMG. There were no significant differences between groups in maternal or neonatal outcomes.
Conclusions
Web-based telemedicine system can be a useful tool facilitating the management of pregnant diabetic patients, as a complement to conventional follow up and could contribute to reduce the outpatient clinic visits.

DOI: 10.1530/endoabs.37.EP477

EP478

Changes in diabetes related quality of life and clinical outcomes in patients with type 2 diabetes, after initiation of injectable treatment

Georgios Georgas
Endocrine Private Clinic, Rhodes, Greece.

In this study, we enrolled 123 patients with DM2 that accordingly to the based on evidence clinical judgment, needed injectable treatment for the achievement of good glycaemic control. There was not significant changes at the whole sample in anthropometrics, but there was increase in insulin treated subgroup and decrease in GLP1 treated subgroup. Glycaemic control was improved ($P<0.001$), without differences between detemir vs glargine subgroups, but with more improvement of HbA1c in insulin treated vs GLP1 treated subgroup ($P<0.05$). Lipid parameters (TC, TG, LDL, and HDL) were improved ($P<0.001$), without changes between the subgroups, except the more significant reduction at TC in insulin treated vs GLP1 treated. No changes were detected at kidney function, neither at the SPP, but there was a reduction at the DPP ($P<0.05$). Hypoglycaemic episodes were increased after injectable treatment at the whole sample, and in the different subgroups, but GLP1 treated patients had less serious hypoglycaemic crisis. There was an improvement at the present quality of life (overview item I), no changes at the quality of live without diabetes (overview item II) and deterioration at the average weighed impact score of the 19 diabetes specific items of ADDQoL19, after commencement of injectable treatment.

DOI: 10.1530/endoabs.37.EP478

EP479

Does a nurse-led Diabetic Renal Clinic improve outcomes?

Susan Irwin, Alvin Shrestha & Parijat De
Department of Diabetes and Endocrinology, City Hospital, Birmingham, UK.

Aim
To audit outcomes and adherence to prescription recommendations in a nurse-led Diabetic Renal Clinic.
Method
Baseline data at time of referral to the clinic was compared to the final clinic visit within a 12-month period (T1) of the first visit (T0), using information from clinic letters and electronic records of patients attending the clinic in our hospital between 2010 and 2014. Patients without at least one follow-up data within a 12-month period were excluded.
Results
We had complete data in 91/208 patients seen. Average age was 63 years and 54 were males. A mean reduction of HbA1c from 74 to 69 mmol/mol ($P=0.01$) was achieved. Systolic blood pressure reduced from 152 to 142 mmHg ($P<0.01$), although no significant change in diastolic blood pressure was seen (75–73, $P=0.113$). Significant urinary albumin:creatinine ratio (ACR) improvement was observed – 53 down to 31 mg/mmol ($P<0.01$). Renal function declined from eGFR 54 to 51 ml/min per 1.73 m^2 ($P=0.001$). There was no significant difference in total cholesterol (4.4–4.3, $P=0.371$). 50 patients (54%) were not on an antiplatelet agent at T1. All of these patients had at least one risk factor (age 50 years or above, systolic BP above 145 or microalbuminuria) and thus aspirin would have been indicated. Six of 17 (35%) patients not on a statin were prescribed one by T1. 79 (86%) were on a lipid-lowering agent at T1. 85% received an ACE inhibitor, ARB, or both.
Conclusion
These results from 1 year follow-up suggests that the nurse-led clinic is effective in reducing HbA1c, systolic blood pressure, and urine ACR levels in this high CV risk patients. This should hopefully result in improved cardiovascular and renal outcomes and appropriate referrals to renal specialist clinic. Most patients received lipid-lowering agents and ACE inhibitors/ARBs, whilst aspirin prescription remained low.

DOI: 10.1530/endoabs.37.EP479

EP480

Effect of liraglutide 1.8 mg in patients with non-controlled type 2 diabetes mellitus at an Endocrinology Clinic: LIED-2 study

Alvaro J Muriel[1], Alvaro A Herrera[2] & Alin Abreu Lomba[2]
[1]Universidad Libre, Cali, Colombia; [2]Centro Médico Imbanaco, Cali, Colombia.

Background and aims
To describe the characteristics of patients with non-controlled type 2 diabetes mellitus with liraglutide treatment.
Materials and methods
Retrospective descriptive study. 85 outpatients (women 49, ages 18–86 years old with non-controlled type 2 diabetes mellitus) were evaluated between July 2013 and March 2014 and received treatment with liraglutide 1.8 mg SQ/day (0.6 mg SQ during the first week, 1.2 mg SQ during the second week, and 1.8 mg during the third week and the rest of the treatment). Age, sex, diagnosis time, weight, HbA1c, fasting glucose, systolic and diastolic blood pressure, pharmacological treatment during 6 months were extracted for analysis.
Results
Patients treated with liraglutide 1.8 mg as monotherapy or in conjunction with a therapeutic scheme decreased HbA1c values at 3 and 6 months (1.02%, 95% CI $\pm$0.93, $P<0.0001$ and 2.08%, 95% CI $\pm$0.8, $P<0.0001$); fasting glucose at 3 and 6 months (37 mg/dl, 95% CI $\pm$33, $P<0.0001$ and 68 mg/dl, 95% CI $\pm$26, $P<0.0001$); weight at 3 and 6 months (3 kg, 95% CI $\pm$10, $P<0.0001$ and 5 kg, 95% CI $\pm$10, $P<0.0001$); SBP at 3 and 6 months (9 mmHg, 95% CI $\pm$15, $P<0.0001$ and 16 mmHg, 95% CI $\pm$16, $P<0.0001$); and DBP at 3 and 6 months (3 mmHg, 95% CI $\pm$6, $P<0.0001$ and 6 mmHg, 95% CI $\pm$6, $P<0.002$). 40% of patients reached HbA1c $<$7.0; 20% reduction of HbA1c, 39% reduction in fasting blood glucose, 6% reduction in mean weight (1–18%, 1–12 kg), 95% reached SBP $<$140 mmHg; 100% reached DBP $<$90 mmHg. Reported adverse events during treatment were nausea (27%), abdominal pain (18%), hypoglycaemia (14%), diarrhoea (9%), and respiratory symptoms (7%). Metformin was present in 65% cases of nausea, 55% cases of diarrhoea, and 43% of cases of abdominal pain. No fatal adverse events occurred.
Conclusion
Patients treated with liraglutide 1.8 mg SQ per day in monotherapy or in conjunction with a therapeutical scheme showed a decrease in HbA1c, fasting glucose, weight, SBP, and DBP during a 6-month treatment.

DOI: 10.1530/endoabs.37.EP480

EP481

Initial experience of SGLT2 inhibitor use in type 2 diabetes

Barbara Cooke, Kathryn Ryan, Mark Gormley & John Lindsay
Mater Infirmorum Hospital, Belfast, UK.

Introduction
SGLT2 inhibitors offer a novel approach to improve glycaemic control in patients with type 2 diabetes through inhibition of renal glucose reabsorption. Phase 3 clinical trials demonstrated consistent glucose lowering effects and weight loss. The objective of our audit was to assess the early effects of treatment with dapagliflozin 10 mg in our clinic population.
Methods
We performed a retrospective audit of clinical parameters in patients ($n=36$, mean age 55.2 years and diabetes mean duration 9.6 years) who attended our hospital in the previous year over a mean follow-up interval of 144 days (25–359 days). 13 patients were previously treated with dual oral agents and 15 with insulin (16–540 units).
Results
We observed a significant improvement in glycaemic control with an HbA1c fall from 85.6 to 72.9 mmol/mol ($P<0.01$). This was accompanied by a mean weight loss of 2.7 kg ($P<0.01$). There was a trend for BP reduction but this was non-significant. No significant correlations were observed between weight loss and other clinical variables. Non-responders were comparable to responders in terms of weight, age, and duration of diabetes. One patient discontinued therapy due to side effects (vulval candidiasis). Improvements in glycaemic control allowed for withdrawal of other agents in three patients including withdrawal of prandial insulin in one individual.
Conclusion
In conclusion, this audit of our early experience with the SGLT2 inhibitor dapagliflozin highlighted clinically meaningful improvements in parameters of glycaemic control, weight, and BMI. Long-term follow up for evidence of sustained drug efficacy in clinical practice is awaited.

DOI: 10.1530/endoabs.37.EP481

EP482

Fungal sinusitis caused by *Aspergillus* in a patient with type 1 diabetes

Goknur Yorulmaz[1], Nurettin Erben[2], Mustafa Acikalin[3], Ercan Kaya[4], Esra Akcan[5] & Nilay Unal Carmik[6]
[1]Department of Endocrinology, Eskisehir State Hospital, Eskisehir, Turkey; [2]Department of Infectious Diseases and Clinical Microbiology, Eskisehir Osmangazi University, Eskisehir, Turkey; [3]Department of Pathology, Eskisehir Osmangazi University, Eskisehir, Turkey; [4]Department of Otorhinolaryngology, Eskisehir Osmangazi University, Eskisehir, Turkey; [5]Department of Radiology, Eskisehir State Hospital, Eskisehir, Turkey; [6]Department of Otorhinolaryngology, Eskisehir State Hospital, Eskisehir, Turkey.

Objective
Aspergillosis is defined as the infection of the *Aspergillus* type mold and is commonly seen in hematologic malignancies, hematopoietic stem cell transplantation, aplastic anemia, primary immunodeficiency, and immunocompromised patients. Fungal sinusitis in diabetes mellitus is generally presented as rhinoorbitocerebral involvement of mucormycosis. Herein, a fungal sinusitis caused by *Aspergillus* case presented with headache is reported.
Case
Twenty-three-year-old male with a history of 9-year diabetes was admitted to our clinic because of high blood glucose level (with a HbA1c level of 14%) and headache which was lasting for 1 month without any pain relief. Cerebral computerized tomography was performed and hyper dens foci fulfilling left maxillary sinus was found. Fungal sinusitis was firstly thought. Tissue sampling from the foci was performed by Ear–Nose–Throat specialist by using endoscopic method. There was no reproduction of any organism in culture but *Aspergillus* hif structure was seen in biopsy sample. Bone destruction or orbital involvement wasn't seen according to radiological findings. Patient was diagnosed as fungal sinusitis. He was empirically treated with itraconazole. His tomography 3 months after the initiation of therapy and there was no sinusitis finding.
Discussion
Rhinocerebral aspergillosis is commonly seen in neutropenic patients whereas mucormycosis is more frequent in diabetic patients. Aspergillosis is detected in a diabetic patient who did not have an additional risk factor. Fungus can colonize in upper and lower airways without causing infection. Only culture positivity is not enough for diagnosis. Invasive fungal sinusitis is diagnosed with the histopathologic evaluation of the biopsy material. Invasive fungal sinusitis is commonly seen in immunosuppressive patients and can cause life threatening conditions. In patients with uncontrolled diabetes and ketoacidosis, invasive fungal sinusitis can be seen.
Conclusion
Although, the most common cause of fungal sinusitis in diabetic patients is mucormycos, *Aspergillus* must be kept in mind.

DOI: 10.1530/endoabs.37.EP482

EP483

Once-weekly exenatide in a real-world clinical setting: clinical outcomes and analysis of potential predictors of response

María del Mar Roca-Rodriguez[1], Jose Carlos Fernandez-Garcia[1], Carmen Maria Cortes-Salazar[2], Isabel Moya-Carmona[3], Ana María Gomez-Perez[1], Isabel Cornejo-Pareja[1], Araceli Muñoz-Garach[1], Maria Molina-Vega[1], Isabel Mancha Doblas[1] & Francisco Tinahones[1]
[1]Endocrinology Department, Virgen de la Victoria University Hospital, Malaga, Spain; [2]Badolatosa Primary Care Centre, Seville, Spain; [3]Pharmacy Department, Virgen de la Victoria University Hospital, Malaga, Spain.

Objective
The aim of this study is to evaluate the effectiveness of once-weekly exenatide on metabolic control, weight, blood pressure, and lipid profile in obese patients with type 2 diabetes (T2DM), and to assess possible predictive factors of response.
Material and methods
Retrospective observational study, conducted with adult obese (BMI ≥ 30 kg/m^2) T2DM subjects that had been initiated once-weekly exenatide following routine clinical practice. Anthropometric measures, blood analysis, and blood pressure measures were collected at the initiation of once-weekly exenatide (V0) and after 16 ± 4 weeks of treatment (V1). Predictors of target metabolic response (HbA1c $<7\%$), were evaluated by using a multiple logistic model.
Results
31 patients were included (mean age 54.4 ± 10.7 years; female 54.8%; and mean duration of T2DM 7.9 ± 5.4 years). Significant changes from V0 to V1 were observed in weight-related parameters (body weight 108.1 ± 28.8 kg vs 101.3 ± 22.3 kg and BMI 41.2 ± 8 kg/m^2 vs 39.3 ± 7.3 kg/m^2, $P<0.001$ for both); HbA1c ($8.6 \pm 1.6\%$ vs $7.3 \pm 1.3\%$, $P<0.001$), lipid profile (total cholesterol 206.4 ± 37 mg/dl vs 181 ± 41.5 mg/dl, $P=0.002$; LDL-cholesterol 124.3 ± 35.8 mg/dl vs 101.6 ± 39.2 mg/dl, $P=0.003$; HDL-cholesterol 39.4 ± 10.7 vs 40.7 ± 10.3, $P=0.331$; and triglycerides 288.1 ± 125.7 mg/dl vs 195.1 ± 80 mg/dl, $P=0.001$). No differences in blood pressure (systolic or diastolic) or number of antihypertensive drugs were found. 45.2% of patients achieved HbA1c $<7\%$, 64.5% lost weight, and 41.9% simultaneously achieved HbA1c $<7\%$ and lost weight. None of the studied variables (age, sex, duration of diabetes, baseline HbA1c, and BMI) were confirmed as predictors of response.
Conclusions
In obese patients with T2DM, once-weekly exenatide increases metabolic control, decreases body weight, and improves lipid profile. However, once-weekly exenatide does not exert beneficial effects on blood pressure. Age, sex, duration of diabetes, baseline HbA1c, and BMI were not predictors of efficacy of once-weekly exenatide.

DOI: 10.1530/endoabs.37.EP483

EP484

Association between peripheral vascular disease and other macrovascular and microvascular complications in diabetic patients

Gonzalo Allo Miguel, Elena García Fernández, Milagros Sierra Bracamonte, Guillermo Martínez Díaz-Guerra & Federico Hawkins Carranza
Endocrinology Service, 12 de Octubre University Hospital, Madrid, Spain.

Introduction
Diabetes mellitus is a condition on the increase, carrying a high risk of macro and microvascular disease. Previous studies suggest a link between microvascular and macrovascular complications in diabetes. However, just a few studies have investigated whether the presence of peripheral vascular disease (PVD) is associated with other macrovascular and microvascular complications in diabetes patients. So, this was the aim of our study.
Patients and methods
98 diabetic patients (68 with type 2 and 20 with type 1 diabetes) were included. PVD was confirmed by arteriography. Other macrovascular complications were collected, including: adverse cardiovascular events (myocardial infarction, angina, etc.) and stroke. Microvascular complications were, also, collected: retinopathy, nephropathy, and peripheral neuropathy.
Statistical analysis
χ^2 test was used to compare the existence of macro and microvascular complications between the groups with and without PVD.
Results
48 males and 50 females with mean age (52.58 ± 20.70) and mean HbA1c ($11.21 \pm 2.33\%$) were included. 14 patients (15.73%) were diagnosed of PVD. The existence of PVD was significantly correlated with the existence of more macrovascular complications ($P<0.001$) and, at least, one microvascular complication ($P<0.005$). Also, significant differences between the groups of patients with or without PVD were found in the rate of neuropathy (78.57 and 23.61%, respectively, $P<0.001$); cardiovascular events (50.00 and 9.59%, respectively, $P=0.002$) and in the rate of strokes (28.57 and 6.67%, respectively; $P=0.01$). There were no significant differences in the rate of retinopathy and nephropathy between both groups.
Conclusions
Our results show significant correlation between the existence of PVD and the existence of more macrovascular complications and one or more microvascular complications. We have found that diabetic patients with PVD present significant higher rates of neuropathy, cardiovascular events and strokes. Despite the limitations of the study, our results suggest that diabetic patients with PVD require proper micro and macrovascular complications screening.

DOI: 10.1530/endoabs.37.EP484

EP485

Diabetic kidney disease and its association with macrovascular disease in diabetic patients

Elena García Fernández, Gonzalo Allo Miguel, Lucas Arroyave Villa, Guillermo Martínez Díaz-Guerra & Federico Hawkins Carranza
Endocrinology Service, 12 de Octubre University Hospital, Madrid, Spain.

Introduction
It is well known that diabetes confers a substantial burden of macrovascular disease. However, just a few studies have investigated the association between

diabetic kidney disease (DKD) and cardiovascular disease. The purpose of this study is to investigate whether the presence of DKD is associated with macrovascular disease in diabetic patients.
Patients and methods
98 diabetic patients (48 males/50 females) were included in the study. DKD was confirmed by the presence of moderately or severely increased albuminuria. Adverse cardiovascular events were collected, including: cardiac events, left ventricular hypertrophy (LVH), peripheral vascular disease (PVD), and stroke.
Statistical analysis
χ^2 test was used to compare the existence of macrovascular complications between groups with and without DKD.
Results
68 patients with type 2 diabetes and 20 with type 1, with mean age (52.58 ± 20.70) and mean HbA1c ($11.21 \pm 2.33\%$), were included in the study. DKD was diagnosed in 24 patients: 16 with moderately increased albuminuria and eight with severely increased. DKD was significantly correlated with the existence of, at least, one macrovascular complication ($P<0.02$). Significant differences between the groups with or without DKD were found in the rate of: cardiac events (32.00 and 9.84%, respectively; $P=0.01$); LVH (36.00 and 1.59%, respectively; $P<0.001$), and PVD (20.00 and 13.33%, respectively; $P=0.04$). These differences remained significant after adjusting for age, sex, hypertension, smoking habit, HbA1c, duration of diabetes, and BMI. No significant differences in the rate of strokes.
Conclusions
Our results show significant correlation between DKD and the existence of one or more macrovascular complications. Moreover, we have found that diabetic patients with DKD present significant higher rates of cardiac events, LVH and PVD than diabetic patients without DKD. Despite the limitations of the study, our results suggest that early detection of DKD might be a valuable component of macrovascular risk assessment in diabetic patients.

DOI: 10.1530/endoabs.37.EP485

EP486

Intensive glycemic control fails to improve indices of vascular dysfunction in patients with type 2 diabetes; results at 6–12 months follow-up

Sofia Antoniou[1], Katerina Naka[2], Aris Bechlioulis[2], Lampros Michalis[2], Agathocles Tsatsoulis[1] & Stelios Tigas[1]
[1]Department of Endocrinology, University of Ioannina, Ioannina, Greece; [2]Department of Cardiology, University of Ioannina, Ioannina, Greece.

Background
In subjects with long duration of type 2 diabetes (T2DM), strict glycaemic control fails to decrease the incidence of cardiovascular disease (CVD). Impaired vascular indices have been associated with adverse cardiovascular prognosis in T2DM. We examined whether intensive glycaemic control in T2DM patients improves vascular indices.
Methods
We studied 68 T2DM patients (64 ± 9 years, 52% males, and T2DM duration 14 ± 10 years) with poor glycaemic control (HbA1c $\geq 7.5\%$), at baseline and 6–12 months after intensive treatment to achieve optimal glycaemic control. Brachial artery flow-mediated dilation (FMD), carotid–femoral pulse wave velocity (PWV), central augmentation index (AIx), large and small artery elasticity indices, common carotid intima–media thickness (cIMT), and ankle–brachial index were measured.
Results
Improvement of HbA1c $>0.5\%$ was achieved in 55 (81%) patients (HbA1c decrease from 9.6 ± 1.8 to $7.3 \pm 1.0\%$, $P<0.001$). In this group of patients, triglycerides decreased (177 ± 140–137 ± 73 mg/dl, $P=0.008$), cIMT increased (0.70 ± 0.20–0.74 ± 0.22 mm, $P=0.038$), and large artery distensibility decreased (14.2 ± 5.2–12.4 ± 4.1 AU, $P=0.045$) at follow-up, while no other changes in vascular indices, blood pressure, lipids, or other laboratory values were found. No difference in vascular indices' changes at follow-up was observed between patients with or without improved glycaemic control (repeated measures (RM)-ANOVA, $P=$NS for all). When patients with improved glycaemic control were compared based on T2DM duration, AIx was decreased in those with short disease duration (<5 years), while it remained unchanged in those with >5 years duration (RM-ANOVA, $P=0.013$).
Conclusions
In T2DM patients, agressive glycaemic control without concomitant improvement in other cardiovascular risk factors was not associated with an improvement in vascular function indices at 6–12 months. However, in patients of <5 years duration, intensive glycaemic control improved only augmentation index, a combined index of aortic stiffness and peripheral vascular function. Multifactorial interventions of longer duration are needed to improve cardiovascular risk in T2DM.

DOI: 10.1530/endoabs.37.EP486

EP487

Intraocular pressure change during oral glucose tolerance test in non-diabetic individuals

Pinar Yildiz[1], Medine Nur Kebapci[2], Fezan Mutlu[3], Harun Servet Yasar[4] & Nilgun Yildirim[4]
[1]Department of Internal Medicine, Eskisehir Osmangazi Medical Faculty, Eskisehir, Turkey; [2]Department of Endocrinology, Eskisehir Osmangazi Medical Faculty, Eskisehir, Turkey; [3]Department of Biostatistics, Eskisehir Osmangazi Medical Faculty, Eskisehir, Turkey; [4]Department of Ophtalmology, Eskisehir Osmangazi Medical Faculty, Eskisehir, Turkey.

Introduction
A significance of chronic hyperglycaemia related to the rising intraocular pressure are discussed in the previous studies. The purpose of the present study was to investigate changes of intraocular pressure induced by acute changes of glucose levels during oral glucose tolerance test in non-diabetic subjects.
Methods
Fifty-one individuals who were needed to be screened for diabetes, were scheduled for oral glucose tolerance test according to the World Health Organization criteria. Biochemical parameters associated with metabolic syndrome, insulin resistance (HOMA-IR) and systolic and diastolic pressure were also measured. Complete ophthalmologic examination was performed before the test. The inclusion criteria were having a normal intraocular pressure (<21 mmHg), and having no eye disease, no ophthalmic surgery or no glaucomatous optic nerve appearance. During the test, intraocular pressure was measured by using rebound tonometry (ICARE) two times at the fasting state and at first and second hours after oral glucose administration.
Results
The mean age of the patients was 46.24 ± 11.31 years. The mean BMI was 29.63 ± 5.25 kg/m^2. The median fasting glucose and intraocular pressure for right was 100 mg/dl (91.250–105.750) and 17 mmHg. The median glucose and intraocular pressure level for right eye in the first hour and in the second hour in OGTT were 153 mg/dl (123.5–190.5), 18 mmHg (14–22) and 117 mg/dl (92.25–140) and 18 mmHg (14–20.75) respectively. The intraocular pressure right eye were significantly higher in the first hour compared to the fasting values ($P<0.05$).
Conclusion
The relation between diabetes mellitus and glaucoma has been addressed in many studies with no clear underlying mechanisms. In our study on healthy non-diabetic individuals, acute hyperglycaemia has found to have a positive relationship with intraocular pressure, suggesting that acute hyperglycaemia may represent a possible mechanism.

DOI: 10.1530/endoabs.37.EP487

EP488

Hypoglycaemia due to drug interaction with clarithromycin

João Silva, Catarina Ivo, Mafalda Marcelino, Luís Lopes, Dolores Passos, Hélder Simões & João Jácome de Castro
Armed Forces University Hospital, Lisbon, Portugal.

Introduction
Interaction between diabetes mellitus (DM) and an infection usually results in hyperglycaemia. However, there is data describing hypoglycaemia events related with the association between certain antibiotics and oral anti-diabetic drugs or insulin.
Case report
Male, 73 years old, with history of hypertension, obesity and dyslipidaemia. DM type 2 was diagnosed 13 years ago with any macro or microvascular complications so far. Currently he's treated with insulin detemir ($40+28$U) and vildagliptin + metformin 50/1000 2id, maintaining good metabolic control (HbA1c 6.9%) with rare episodes of hypoglycaemia. Owing to dental abscess he started a treatment with clarithromycin 500 mg bid. After 36 h of taking the drug, referred two episodes of night symptomatic hypoglycaemia, on consecutive days (42 and 37 mg/dl respectively), which reversed after sugar intake. In this context, he went to our clinic, and the antibiotic was changed to amoxicillin + clavulanic $850+125$ mg, keeping the usual therapy for DM. There weren't any more episodes of hypoglycaemia.

Conclusions
In the literature there are few reports of hypoglycaemia induced by clarithromycin in combination with insulin detemir. 40–70% of clarithromycin circulates bound to proteins, which can dissociate insulin detemir of protein binding sites (98% binds to albumin), increasing the free concentration and its pharmacological effects. This phenomenon can cause a faster beginning of action, simulating an insulin with intermediate or short-action, leading to hypoglycaemia. Clarithromycin is a potent inhibitor of CYP3A4. Vildagliptin isn't a substract of this cytochrome. Metformin is a substract of this cytochrome's family, but there isn't any report of hypoglycaemia with this association.
Clinicians should be aware of this drug interaction, regarding the need of adjustments of insulin doses to avoid possible adverse effects and hospitalizations. Patients who start clarithromycin should be advised to have more frequent monitoring capillary blood glucose and re-educated about the signs, symptoms, and treatment of hypoglycaemia.

DOI: 10.1530/endoabs.37.EP488

EP489

Insulin oedema in newly diagnosed type 1 diabetes patient: a case report

Ayten Oguz[1], Dilek Tuzun[1], Murat Sahin[1], Didem Atay[2], Berivan Ganidagli[2], Safa Ersen Ganidagli[2] & Kamile Gul[1]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey; [2]Department of Internal Medicine, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey.

Aim
In this case report we present a newly diagnosed, underweight type 1 diabetes mellitus (DM) patient developed insulin oedema following high dose insulin therapy.
Case
A 18-year-old male patient was admitted to the hospital with a 1-month history of excessive water consumption, pollakiuria, polyuria, and weight loss 6 kg. In laboratory examination, hyperglycaemia and ketonuria were detected; arterial blood pH was 7.38. Patient was hospitalised to the Endocrinology Clinic with a diagnosis of type 1 DM with ketosis. The patient was initially treated with an i.v. infusion of insulin and isotonic saline for hyperglisaemia and ketonuria. After clinical improvement basal-bolus therapy was started. At the follow-up visits, insulin requirement increased to $\sim$2 U/kg per day. 15 days after discharge, the patient was again admitted to the clinic with a swelling in both legs. The patient had pitting pretibial and ankle oedema in both extremities. In laboratory examination, hyperglycaemia (fasting blood glucose 211 mg/dl), mild hypoalbuminaemia (3.5 g/dl) were detected. Other biochemical blood test results were normal. Patient was hospitalized again. No proteinuria was detected in his urine. Chest X-ray, echocardiography, abdominal and lower extremity Doppler ultrasonography results were also within normal limits. So as a result of these examinations, other factors that could cause oedema have been ruled out. Basal-bolus therapy was continued. At the follow-up visits, his insulin need was observed to decline (1.5 U/kg per day). With reduced insulin doses, oedema regressed spontaneously.
Conclusion
Oedema formation is one of the rare complications of insulin therapy. The cause and incidence rate of insulin oedema are not clearly defined. The cause of this condition is not exactly known. In case of a catabolic state due to lack of insulin, intensive fluid therapy may lead to liquid extravasation in subcutaneous tissue and this may result in peripheral oedema. This condition can also worsen due to increased capillary permeability caused by chronic hyperglycaemia. In this case report we present a newly diagnosed, underweight type 1 DM patient developed insulin oedema following high dose insulin therapy.

DOI: 10.1530/endoabs.37.EP489

EP490

Associations of serum magnesium levels with diabetes and diabetic complications

Dilek Arpaci[1], Aysel Gurkan Tocoglu[1], Hasan Ergenc[1], Sumeyye Korkmaz[1], Aysenur Ucar[1], Atilla Onmez[1], Mehmet Yildirim[1], Ozlem Hurmeydan[2] & Ali Tamer[1]
[1]Department of Internal Medicine, Sakarya Education and Research Hospital, Sakarya University, Sakarya, Turkey; [2]Department of Biochemistry, Sakarya Education and Research Hospital, Sakarya, Turkey.

Background
Magnesium (Mg) deficiency is a common problem in diabetic patients. Deficiency of Mg may increase the incidence of diabetes. Development of hypomagnesemia may affect glycaemic regulation and trigger complications of diabetes. The aim of our present study was to explore relationships between the serum Mg level and diabetes complications.
Materials and methods
In this retrospective study, we evaluated 673 diabetic patients, of whom 57.8% were males and 42.2% females. Mean patient age was 55.6 years and the mean duration of diabetes 81 ± 86.9 months.
Results
The mean level of HbA1c was $9.0 \pm 2.4\%$ (4.5–18); the mean serum creatinine level 0.83 ± 0.22 mg/dl (0.3–1.5); and the mean Mg level 1.97 ± 0.25 (1.13–3.0) mg/dl. Total of 55 (8.2%) patients had diabetic retinopathy and 95 (14.1%) diabetic neuropathy. Of all patients, Five hundred patients 74.3% of patients had normoalbuminuria, 133 19.8% of microalbuminuria, and 40 5.9% of overt proteinuria. 171 patients (25.4%) had HbA1c levels equal or below 7%; and 502 patients (74.6%) had HbA1c levels above 7%. The patients were divided into two groups in terms of their serum Mg levels; low-level ($\leq$1.8 μg/dl) and normal (1.9–2.6 μg/dl). No between-group difference in any of BMI, fat mass, total body water (TBW), fasting glucose (FG) level, lipid parameters, sodium or potassium levels, or glomerular filtration rate (GFR), was apparent. Although, the groups did not differ in terms of retinopathy or neuropathy levels, microalbuminuria was more common in hypomagnesemic patients ($P=0.004$). HbA1c levels did not differ between the groups ($P=0.243$). However, a weak negative correlation was apparent between serum Mg and HbA1c levels ($r=-0.110$, $P=0.004$) and also between serum Mg level and overt proteinuria ($r=-0.127$, $P=0.018$).
Conclusion
Mg depletion is a common problem in patients with diabetes mellitus. It affects both glycaemic regulation and emergency of complications. Serum Mg level affected both glycaemic regulation and the extent of emergency diabetic complications. Also, poor glycaemic regulation affected serum Mg levels.

DOI: 10.1530/endoabs.37.EP490

EP491

Scleredema in a patient with long-standing type 2 diabetes mellitus

Isilay Kalan Sari[1,2], Senay Arikan Durmaz[2], Önder Bozdogan[3], Mukadder Kocak[4] & Ramazan Cosar[5]
[1]Department of Endocrinology and Metabolic Diseases, Burdur State Hospital, Burdur, Turkey; [2]Department of Endocrinology and Metabolic Diseases, Faculty of Medicine, Kirikkale University, Kirikkale, Turkey; [3]Department of Pathology, Faculty of Medicine, Kirikkale University, Kirikkale, Turkey; [4]Department of Dermatology, Faculty of Medicine, Kirikkale University, Kirikkale, Turkey; [5]Department of Internal Medicine, Faculty of Medicine, Kirikkale University, Kirikkale, Turkey.

Introduction
Scleredema is a rare skin disease, clinically presents as diffuse, painless induration, and thickening of skin. It primarily affects the upper part of body and usually occurs in association with diabetes mellitus, infections or monoclonal gammopathy. We discussed a case of scleredema in patient with history of diabetes mellitus.
Case report
A 54-year-old woman with history of long-standing, poorly-controlled diabetes mellitus, hypertension, and coronary artery disease was referred to our department. She complained to gradually-developing several months, and hardening erythematous plaques on the neck and upper back. Her medication included metformin (2000 mg/day) and premixed insulin (50 U/day). Physical examination revealed edematous, erythematous plaques on posterior neck and upper back. Other systemic evaluations were normal. Complete blood count and comprehensive biochemical panel were normal, exception of fasting blood glucose of 277 mg/dl. HbA1c was 11.8%. The patient was examined by dermatologist and skin biopsy was performed. On histopathological examination; epidermis was normal but there is prominent separation of collagen fibres throughout the dermis, thickening of the dermis and coarsening of collagen. Focal alcian blue positive mucine was also detected. Histopathological findings were consistent with scleredema. She had shown no infection signs. Scleredema was thought to be secondary to diabetes. She was started on intensive insulin regimen and glucose levels decreased within normal range. She was started on local PUVA therapy. After 2 months; redness and oedema of skin has partially disappeared, mobility of the back improved and skin of upper back was softer.
Conclusion
Scleredema diabeticorum is a rare complication of diabetes and reveals in obese subjects with long standing and poorly controlled diabetes mellitus. It can be clinically and histopathologically differentiated by other fibrosing disorders.

Tight glycaemic control is recommended but efficiency has not been proven. Ultraviolet A-1 phototherapy and PUVA seem to be most effective treatments for this disease.

DOI: 10.1530/endoabs.37.EP491

EP492

Coated pellets with controlled glucose release for interdiction of hypoglycaemia in children with diabetes

David Neumann[1], Aleš Franc[2], Jan Muselík[2] & Dana Sabadková[2]
[1]University Hospital Hradec Kralove, Hradec Kralove, Czech Republic; [2]University of Veterinary and Pharmaceutical Sciences, Brno, Czech Republic.

Introduction
A diet plan, meals with suitable glycaemic index and sophisticated insulin delivery are used for balanced sacharides–insulin intake. In specific real day-to-day life situations patients must break their activities. Urgency to east in socially inappropriate time harm their lives, especially in young children with diabetes. Night hypoglycaemia, a parental fear of insufficient snack in nursery, sports with prolonged race periods, etc. are among these situations. Controlled glucose release formulation with 2, 4, and 6 h lag time offers chance to substitute snacks or other meals in advance, allowing to decrease life inconvenience and improve therapy adherence of children with diabetes and their parents.
Design
A dosage form with controlled glucose release was prepared, a release period of 2–4 h was achieved. Optimal diameter, resistance of the coat, volume, taste, and acceptable form to swallow were refined in pharmaceutical treat.
Results
An amount of two exchange units is easy to add to standard meals, e.g. yoghurt. Pellets (clinically powder) do not cause abdominal discomfort. In CGM studies, formulation prevent night hypoglycaemia.
Conclusions
The formulation with controlled glucose release with specific easy-to-explain lag time offers additional means for diabetes treatment.
Disclosure
This work was supported by Grant of IGA Ministry of Health of Czech Republic NT14479/2013.

DOI: 10.1530/endoabs.37.EP492

EP493

Different glycaemic patterns in patients with steroid diabetes and type 2 diabetes

Andreja Maric & Bozidar Poljak
County Hospital Cakovec, Cakovec, Croatia.

Introduction
Long-term use of glucocorticoids has impact on reduction of β-cell function and peripheral insulin sensitivity, leading to a steroid diabetes.
Aim
To assess patterns of change of glycaemia and need for insulin at admission to hospital, during days 1–5 and at discharge in patients with newly diagnosed type 2 diabetes (NST) compared with patients with a history of taking corticosteroids and newly diagnosed diabetes mellitus (ST).
Material and methods
Twenty patients with newly diagnosed diabetes were included; ten without, and ten with a history of taking corticosteroids. The day after admission (day 1) basal-bolus insulin scheme was introduced. Bolus insulin was used in the initial dose of 0.05 U/kg per meal, and a basal insulin (NPH) 0.2 IU/kg BW at bedtime. The changes of glycaemia during 1–5 days were observed by measurement of plasma glucose profile before meals and 2 h after/before bedtime, and the need for insulin during the investigated time was recorded. A statistical analysis of data was performed.
Results
12 women (six NST and six ST) and eight men (four NST and four ST) were included in the study. The longest period of taking corticosteroids was 150 days, with a cumulative dose of 9600 mg of methylprednisolone. Statistically significant differences ($P<0.05$) were obtained: in total dose bolus insulin and the number of units per kilogram BW before dinner between NST and ST groups, and in the ST group in the first 5 days of treatment vs. at discharge; changes in plasma glucose in the period after lunch to dinner in ST group. There was a positive correlation between the cumulative dose of corticosteroids and the plasma glucose at admission at women in ST group.
Conclusion
Corticosteroids primarily cause hyperglycaemia in the afternoon and evening, and the targeted treatment and monitoring of glycaemic control should be directed to the above hours.

DOI: 10.1530/endoabs.37.EP493

EP494

Angiopoietin 1 in patients with type 2 diabetes mellitus and diabetic retinopathy

Abd El Sattar El-Deeb[1], Mohamed Halawa[1], Ahmed Saad[2], Inas Sabry[1], Maram Mahdy[1], Mohamed Abd El Aziz[3] & Nagwa Roshdy[1]
[1]Internal Medicine Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt; [2]Ophthamology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt; [3]Biochemistry Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

Background
Diabetic retinopathy (DR) is a clinically well-defined sight-threatening complication in type 2 diabetes. Angiopoietin 1 (Ang1) has been shown to promote endothelial cell survival without causing proliferation, stabilise endothelial interactions with surrounding support cells and can block the vascular permeability effects of vascular endothelial growth factor (VEGF). More recent data suggest that balance between these growth factors may affect vascular endothelial integrity and may be involved in the pathogenesis of diabetic retinopathy.
Aim of the study
To evaluate serum level of Ang1 in patients with DR and its relation to the severity of DR.
Methods
This is a cross sectional study comprised 75 patients with type 2 diabetes mellitus. They were divided into four groups, group A: 25 diabetic patients with proliferative DR (PDR), group B: 25 diabetic patients with non-proliferative DR (NPDR), group C: 25 diabetic patients with normal fundus, and group D: 50 healthy volunteers of matched age and sex.
Results
There was a high statistically significant reduction in serum level of Ang1 in diabetic patients ($622.53+394.94$) than the healthy control group ($1637.00+253.50$), $P<0.001$. Ang1 was significantly lower among group A (PDR) ($330.80+145.19$) than group B (NPDR) ($489.60+226.89$), and group C ($1047.20+336.83$). Correlation between Ang1 vs the other variables showed a highly significant negative correlation between Ang1 and HbA1c ($P<0.001$) and a significant negative correlation with albumin/creatinine ratio (ACR), $P<0.02$.
Conclusion
There is a significant reduction in serum Ang1 in patients with DR and correlated with the severity of DR. This reduction of Ang1 may reflect a role in the pathogenesis and progression of DR.

DOI: 10.1530/endoabs.37.EP494

EP495

Eighteen grams of glucose are necessary to treat severe hypoglycaemia: experience from the Emergency Medical Services Department

Charlotte Cohen[1,3], Marinos Fysekidis[3], Célia Etiennar[1], Lucie Ginaux[1], Jean-Luc Sebbah[1], Régis Cohen[2] & Philippe Lakhnati[1]
[1]SMUR Centre Hospitalier de Gonesse, Gonesse, France; [2]Hopital Delafontaine, Saint Denis, France; [3]Hôpital Avicenne, Bobigny, France.

We know that non-severe hypoglycaemia (SH) should be treated with the immediate intake of 15–20 g of oral glucose, there are no data according to our knowledge in the current literature for the dose of glucose that is necessary to inject in SH. We have analysed retrospectively the treatment of pre hospital SHs as reported after an emergency call for intervention. Our primary objective was to know the dose of the given glucose and our secondary objective was to know the factors involved in determining these doses. Between April 2012 and December 2013 148 cases with SH were analysed retrospectively. A total of 104 cases (77 patients) were included in the final analysis, there were 29 women, patients had a mean age of 62 ± 19 years and 62/77 were on insulin therapy. The kidney function, the insulin dose and the duration of symptoms on arrival was unknown in most cases. Almost half of the patients (49.53%) were admitted in the nearby hospital. after the intervention Patients that were not admitted had a pasta meal. Average blood glucose on arrival was 29 and 121 mg/dl at the departure of the emergency team. The average dose of injected glucose was 18 g (range 6–69 g)

according to the following procedure (first injection, 7 g glucose; second, 6 g; third, 5 g; mean glucose levels were 83 ± 33 for second and 108 ± 57 mg/dl for the third injection). The administered dose was inversely correlated with the duration of the intervention ($\beta = -0.267$, $P = 0.007$) and the Glasgow index ($\beta = -0.357$, $P = 0.001$) even after adjustment for patient's age. It seems that treatment is guided from the clinical severity of consciousness and can be treated injecting 60 ml glucose 30% (18 g of glucose), for most patients.

DOI: 10.1530/endoabs.37.EP495

EP496

SUMO4 163G > A variation is associated with kidney disease in type 2 diabetes in Indian population

Vinod Kumar[1], Nisha Sinha[1], Ashok K Yadav[1], Anil Bhansali[2], Pinaki Dutta[2] & Vivekanand Jha[1]
[1]Department of Nephrology, Postgraduate Institute of Medical Education and Research, Chandigarh, India; [2]Department of Endocrinology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Background
Various genetic and environmental factors are appear to contribute to the development of kidney disease in type 2 diabetes. Small ubiquitin-related modifier 4 (SUMO4) appear to play a role in development and/or progression of diabetic nephropathy. Substitution of methionine with valine at codon 55 (M55V) of SUMO4 enhances activity of nuclear factor-kB, a central mediator of inflammation proapoptotic events.
Aims
To investigate the association between the SUMO4 M55V (rs237025, 163G > A) variant and kidney disease in north Indian individuals with type 2 diabetes.
Materials and methods
A case–control analysis was performed using genomic DNA samples from 201 subjects with diabetic nephropathy (DN) and 216 patients with diabetes but no kidney disease (DM). The SUMO4 163G > A polymorphic region was amplified using PCR and genotyping was done by digestion of amplified PCR product with restriction enzyme MseI.
Results
The duration of diabetes was higher in DN compared to DM ($P = 0.001$). Clinical characteristics like blood pressure, cholesterol, triglycerides, HbA1c, and serum creatinine were significantly different between the two groups ($P < 0.001$). The frequency of other diabetic complication like neuropathy and retinopathy was also significantly greater in DN ($P < 0.001$). The genotypic and allelic frequencies of the studies variant were significantly different in DM and DN groups. GG genotype and G allele were significantly more frequent in DN as compared to DM ((GG: $P = 0.018$, OR = 1.72, 95% CI 1.1–2.7) (G: $P = 0.017$, OR = 1.4, 95% CI 1.1–1.8)).
Conclusions
This study shows that SUMO4 163G > A polymorphism might be associated with susceptibility to diabetic nephropathy.

DOI: 10.1530/endoabs.37.EP496

EP497

Feasibility, acceptability, and uptake rates of gestational diabetes mellitus screening in primary care vs secondary care: findings from a randomised controlled mixed methods trial

Marie Tierney, Angela O'Dea, Andriy Danyliv, Liam Glynn, Brian McGuire, Louise Carmody, John Newell & Fidelma Dunne
National University of Ireland, Galway, Ireland.

Introduction
It is postulated that uptake rates for gestational diabetes mellitus (GDM) screening would be improved if offered in a setting more accessible to the patient. However, this has not been previously investigated, nor has the feasibility or the acceptability of such an alternative. The aim of this study is to evaluate the rate of uptake of GDM screening in the primary vs secondary care setting, and to qualitatively explore the providers' experience of primary care screening provision.
Methods
This mixed methods study was composed of a quantitative unblinded parallel group randomised controlled trial and qualitative interview trial. 781 pregnant women were randomised to receive a 2-h, 75 g oral glucose tolerance test in either the primary ($n = 391$) or secondary care ($n = 390$) setting. Semi-structured interviews with 13 primary care providers were conducted.
Results
Statistically significant differences were noted between the two quantitative study arms for uptake rates (52.7% in primary care compared to 89.2% in secondary care; $P < 0.001$), crossover rates (32.5% in primary care compared to 2.3% in secondary care; $P < 0.001$), and non-uptake rates (14.8% in primary care compared to 8.5% in secondary care; $P = 0.005$). Of the total potential participants, 37.2% ($n = 1206$) could not be involved as their primary care provider did not engage with the trial. Primary care providers reported difficulties with the conductance of GDM screening citing workload, logistical challenges and lack of remuneration as problematic, while recognising primary care as the most appropriate and preferable location for screening.
Conclusions
Currently, provision of GDM screening in primary care in Ireland, despite its acknowledged benefits, is unfeasible due to poor uptake rates, poor rates of primary care provider engagement and primary care provider concerns, particularly with regard to resourcing limitations.
Disclosure
This work was supported by the Health Research Board of Ireland (grant number ICE/2011/3).

DOI: 10.1530/endoabs.37.EP497

EP498

Real-time sonoelastography and ultrasound evaluation of Achilles tendon of diabetic patients

Berna Evranos[1], Ilkay Idilman[2], Ali Ipek[2], Sefika Burcak Polat[1], Bekir Cakir[1] & Reyhan Ersoy[1]
[1]Endocrinology and Metabolism Department, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey; [2]Radiology Department, Ataturk Education and Research Hospital, Ankara, Turkey.

Introduction
Diabetes mellitus (DM) is an endocrine disease characterised by metabolic abnormalities and long-term complications. Achilles tendon (AT) play an important role in foot biomechanics. We aimed to investigate the effect of DM on the AT, which may contribute to the long-term complications in the foot–ankle complex.
Materials and methods
78 diabetic patients with (35 cases) or without (43 cases) diabetic foot ulcers were recruited from Endocrinology Clinic. Thirty-three age, gender, and BMI matched non-diabetic healthy individuals with no history of Achilles tendinopathy were selected among hospital staff as controls. All participants underwent ultrasonography and sonoelastography of their ATs for evaluating AT thickness (ATT) and stiffness (ATS). Each patient was also tested for fasting plasma glucose (FPG) and HbA1c as a measure of diabetes control. Other chronic complications were also evaluated in all diabetic patients.
Results
The AT was significantly thicker in the diabetic patients with diabetic foot ulcers compared to diabetics without any ulcer and the controls ($P < 0.001$). The ATT correlated with the BMI ($r = 0.224$, $P = 0.04$) and age ($r = 0.419$, $P = 0.001$). HbA1c, FPG, and duration of diabetes were higher for diabetic patients with foot ulcers. We observed that the ATT values were positively correlated with neuropathy ($P = 0.001$), retinopathy ($P = 0.001$), nephropathy ($P = 0.006$), peripheral arterial disease ($P = 0.001$), and coronary arterial disease ($P = 0.005$) in diabetic patients without foot ulcers. But this correlation wasn't detected for diabetic patients with foot ulcers. ATS decreased in the diabetic patients with diabetic foot ulcers.
Conclusion
Diabetic patients with diabetic foot ulcers have softer and thicker AT then the other diabetics and healthy controls. This is the first study reported that research sonoelastosonography of AT of diabetic patients.

DOI: 10.1530/endoabs.37.EP498

EP499

Effect of gemigliptin switching from pioglitazone with metformin in type 2 diabetes

Yonghyun Kim & Donghyun Shin
Bundang Jesaeng Hospital, Seongnam, Kyeonggido, Republic of Korea.

The DPP4 inhibitors that increase insulin secretion by glucose dependently can also relieve insulin resistance because they improve early phage insulin secretion and prevent late hyperinsulinaemia. It also can be more effective in controlling the blood glucose because it acts synergistically with metformin by improving insulin secretory dysfunction compared TZD with metformin that has similar action mechanism. One of those is gemigliptin that was developed in this country recently and there are not many clinical studies. So, we observed the effect of gemigliptin with metformin compared to pioglitazone with metformin. We recruited 81 type 2 DM who failed in glucose control target below 7% of HbA1c or have side effect such as weight gain with metformin plus pioglitazone. The 15 mg of pioglitazone was used when it was switched because the usual dose permitted by national insurance was 15 mg at that time. Pioglitazone was switched to gemigliptin without changing the dose of metformin. The mean HbA1c level of 3 months and just before switching was compared to the mean of 3 and 6 months after switching. The difference of weight and HOMA-IR just before and 6 months after switching was also compared. The age was 56.4 ± 10.0 and mean BMI was 26.3 ± 5.4. The mean HbA1c level before switching was 7.1 ± 4.46. The HbA1c level was decreased in 72 patients (89%). The mean decrement of HbA1c was 0.58 ± 0.39 in above group. The body weight was increased (1.2 ± 0.39 kg) in 27 (33%) and decreased (2.9 ± 2.58 kg) in 48 (59%). The mean BMI was lower in weight gain group (24.1 ± 9.7) than in weight loss group (29.0 ± 5.5). The mean HOMA-IR before switching was 2.54 ± 2.55. HOMA-IR was increased in 67% and mean was 1.51 ± 1.47. It was decreased in 33% and mean was 0.43 ± 0.16. The gemigliptin can be a good substitute to improve glucose control when failed with 15 mg of pioglitazone with metformin. It is more effective in weight control especially in high BMI group.

DOI: 10.1530/endoabs.37.EP499

EP500

Cytokine status and subpopulations of peripheral blood lymphocytes in patients with type 2 diabetes mellitus and non-alcoholic fatty liver disease

Kateryna Kondratiuk[1], Petro Bodnar[1], Mykola Lysianyj[2], Liudmyla Belska[2] & Antonina Potapova[2]
[1]Bogomolets National Medical University, Kyiv, Ukraine; [2]Romodanov Institute of Neurosurgery, Kyiv, Ukraine.

One of the leading roles in the mechanisms of type 2 diabetes mellitus (T2DM) belongs to immunopathological link of pathogenesis, which determines the development rate and severity of its specific complications, in particular, non-alcoholic fatty liver disease (NAFLD).

The purpose

To examine the contents of cytokines and major lymphocyte subsets in patients with T2DM and NAFLD.

Description of methods

We observed 118 patients, including 64 patients with T2DM and NAFLD, 26 patients with T2DM and 28 patients with NAFLD. The control group consisted of 25 apparently healthy individuals.

Results

Identified changes in the level of cytokines and lymphocyte subpopulation composition in combination of T2DM with NAFLD can be used both for diagnosis and for predicting adverse development of this disease, in particular the development of the inflammatory response in the liver (increased level of IL1β), intensity and orientation of immunopathological reactions (increased IFNγ level, decreased IL4 level, and changed NK cells level), the intensity of proliferation of connective tissue and fibrosis formation (increased IL10 level).

Conclusions

In patients with T2DM, NAFLD or a combination of these abnormalities are observed changes in cytokine status, reflecting the intensity of the inflammatory immune responses, their direction and possible forecast of liver fibrosis. Increased blood levels of IL1β, IL17, and IFNγ indicate the presence of high inflammatory and immunopathological reactions in patients with T2DM and NAFLD. Imbalance is observed in the composition of lymphocyte subpopulations, manifested by decries of CD8+ and CD16+ lymphocytes at a relatively stable level of T helper (CD4+) lymphocytes and increased content of CD20+ lymphocytes which develops against the background of increased level of circulating immune complexes. In patients with NAFLD and T2DM increased apoptotic preparedness of lymphocytes were revealed, which manifests as increased content of CD95+ cells in the blood.

DOI: 10.1530/endoabs.37.EP500

EP501

Evaluation of violation vibration sensitivity for early diagnosis of diabetic distal polyneuropathy in patients with type 1 diabetes in the Republic of Belarus

Shepelkevich Alla[1], Bilodid Irina[1], Sosedkova Alexandra[1], Salko Olga[2], Malkevich Alexandra[1], Volkov Nikita[1] & Yurkovec Vladislav[1]
[1]Belarusian State Medical University, Minsk, Belarus; [2]Republic Medical Rehabilitation and Balneo Treatment Cente, Minsk, Belarus.

Screening for diabetic polyneuropathy (DP) is advisable for all patients with type 1 diabetes mellitus (T1DM) after 5 years the detection of the disease. The aim of the study was to evaluate the vibration sensitivity disorders in T1DM patients using Vibratip device for early diagnosis of DP.

Materials and methods

509 patients with T1DM (224 women and 285 men) (mean age: 28.5 ± 8.5 years, mean BMI −24.2 ± 4.1 kg/m^2) were examined. The research was conducted within the framework of the republic action 'optimization of approaches to improve the early diagnosis and prevention of diabetic polyneuropathy'. According to the criteria for inclusion in the research were examined patients with T1DM duration of disease is not more than 5 years (duration of DM: 3.3 ± 1.6 years). During the campaign was carried out a survey in individuals who seek health care institutions of the Republic of Belarus, the analysis of the medical documentation and examination of patients with an estimate of the sensitivity stop using the device Vibratip.

Results

The most common clinical symptoms of DP were: pain – 69 (13.6%) patients, burning – 83 (16.3%), numbness – 134 (26.3%), feeling of pins and needles – 132 (25.9%), and feeling of electric shock – 25 (4.9%) in patients with T1DM. Sensory disturbances feet were found in 23.6% (120) of diabetic patients: 12.6% (64) women and 11% (56) males using Vibratip device.

Conclusions

The data confirmed the high incidence of violation of vibration sensitivity in patients with T1DM with disease duration of <5 years.

DOI: 10.1530/endoabs.37.EP501

EP502

Disabilities of the arm, shoulder, and hand (DASH) questionnaire and diabetic complications: preliminary results

Dilek Tuzun[1], Emine Duygu Ersozlu Bozkirli[2], Ayten Oguz[1], Murat Sahin[1], Hanife Bolat[3], Mustafa Saygin Deniz[3], Omer Faruk Akgul[3] & Kamile Gul[1]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey; [2]Division of Rheumatology, Adana Numune Training and Research Hospital, Adana, Turkey; [3]Department of Internal Medicine, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey.

Aim

Disabilities of the arm, shoulder, and hand (DASH) questionnaire is a self-administered region-specific outcome instrument developed as a measure of self-rated upper-extremity disability and symptoms. The DASH consists mainly of a 30-item disability/symptom scale. In this study, we aimed to evaluate DASH questionnaire in 1000 type 2 diabetes mellitus (T2DM) patients.

Material and methods

297 patients (mean age 52.13 ± 9.37 years, 190 women and 107 men) who had T2DM were included as a preliminary in this study. The presence of cheiroarthropathy, Dupuytren's contracture, tinnel sign, and tendinitis was assessed. Diabetic retinopathy was assessed by direct ophthalmoscopy. Urinary albumin excretion was determined in at least two 24 h urine samples. DASH questionnaire was administered to the diabetic patients. Direct measurements of parameters were performed with a Tanita body composition analyser. The bioimpedance parameters we measured were body fat percentage (%BF), total body fat (TBF, kg), and BMI.

Results

The mean diabetic duration was 7.71 ± 6.28 years. Dupuytren's contracture was present in 7.7%, cheiroarthropathy in 11.1%, tinnel sign in 19.5%, and tendinitis in 4.4%. Retinopathy was present in 15.5%, nephropathy in 18.2%. DASH score was 68.00 ± 31.70. Mean BMI was 32.28 ± 5.80. Mean TBF was 29.222 ± 11.77 kg. Mean %BF was 34.00 ± 10.19. There was positive correlation between DASH score and cheiroarthropathy, tinnel sign, and tendinitis ($P = 0.006$, $r = 159$; $P = 0.000$, $r = 214$; and $P = 0.004$, $r = 168$ respectively). There was positive correlation between DASH score and BMI and TBF and %BF ($P = 0.000$, $r = 288$;

$P=0.000$, $r=284$; and $P=0.000$, $r=319$ respectively). No correlation was found between DASH score and diabetic nephropathy and retinopathy.
Conclusions
DASH questionnaire is useful instrument for measuring functional disability in upper extremity complaints of diabetes mellitus patients. It should also be taken into consideration in order to increase the quality of life in DM patients.

DOI: 10.1530/endoabs.37.EP502

EP503

Can the onset of type 2 diabetes be delayed by a group-based lifestyle intervention in women with prediabetes following gestational diabetes mellitus? Findings from a randomised control mixed methods trial

Angela O'Dea[1], Marie Tierney[1], Brian McGuire[1], John Newell[1], Irene Gibson[2], Liam Glynn[1], Eoin Noctor[1], Susan Connolly[3] & Fidelma Dunne[1]
[1]National University of Ireland, Galway, Ireland; [2]Croí West of Ireland Cardiac Foundation, Galway, Ireland; [3]Imperial College London, International Centre for Circulatory Health, London, UK.

Aim
The aim of this paper is to report on the outcomes of a randomized controlled trial designed to evaluate the effectiveness of a group-based lifestyle intervention programme for reducing the risk factors associated with diabetes in women with pre diabetes following gestational diabetes. We expected that the group based intervention through its educational and supportive approach would enable improvements in psychosocial health, health behaviours, anthropometry, and glucose function.
Design and methods
A two groups, mixed methods randomized controlled trial in which 50 women with a history of gestational diabetes mellitus (GDM) and abnormal glucose tolerance *postpartum* were randomly assigned to MyAction ($n=24$) or wait control ($n=26$). The primary outcome variable was the change in fasting plasma glucose (FPG) from study entry to 1-year follow-up. Secondary outcomes were: glucose tolerance (2 h), insulin resistance, lipid profile, weight, shape, diet, and exercise levels. The role of mood, cognition and wellbeing were also explored. Post intervention qualitative interviews with participants are also reported.
Results
At 1-year follow-up, the intervention group showed significant improvements over the wait control group on stress, diet self-efficacy, and quality of life. There was no evidence of an effect of the intervention on measures of biochemistry or anthropometry the effect on one health behaviour – diet adherence, was close to significance. For many participants improvements made during the intervention were not sustained in the post intervention period.
Conclusions
Optimal approaches for preventative measures must tackle the barriers to participation faced by this population, home-based interventions should be investigated. Strategies for promoting long-term health self-management need to be developed and tested. The role of psychosocial factors in facilitating health related behaviour change should be explored further.
Disclosure
This work was funded by the Health Research Board of Ireland, Interdisciplinary Capacity Enhancement Grant number ICE/2011/3.

DOI: 10.1530/endoabs.37.EP503

EP504

Topical wound pressurised oxygen therapy: new approach in treatment of diabetic foot ulcers?

Maja Čavlović Naglić, Maja Bakula & Lea Smirčić Duvnjak
Merkur University Clinic, Zagreb, Croatia.

Introduction
Topical wound oxygen therapy (TWO_2) is therapeutic modality that delivers humidified pressurised O_2 directly to the specific body part to achieve tissue penetration and increased O_2 levels to the open ischaemia wound. O_2 is vital in the synthesis of collagen, enhancement of fibroblasts, angiogenesis, leukocyte function, energy metabolism, and the inhibition of mycrobial growth. TWO_2 therapy has showed effectiveness as an adjunctive therapy for the management of acute and chronic diabetic foot ulcers, venous stasis ulcers, pressure ulcers, and mixed ulcers.
Materials and methods
Five male patients aged 50–77 years with chronic diabetic foot ulcers grade 2A or worse according to the University of Texas wound Classification system (UTI) and ankle–brachial index (ABI) at least 0.5 in the affected limb were treated with TWO_2 60 min daily, Monday through Friday for 6 weeks. Wound size measuring, microbiological samples, and digital photography of the wound were done once weekly. Wounds were debrided prior to therapy by the vascular surgeon, who assessed the wound every 7–10 days and debrided it if necessary. If infection was present antibiotics were given according to the antibiogram.
Results
Wound area reduced from average 8.86–2.54 cm^2. Ulcer classification changed from UTI 2-B, 2-C and 2-D to 1-A and 0-A. Infection was absent in all wounds comparing to four infected wounds at the beginning.
Conclusion
Although current studies have shown effectiveness of TWO_2 in treatment of diabetic foot ulcers, there are no specific cost effectiveness studies completed and there have been no studies found that show improved quality of life for patients receiving TWO_2. The most important thing is that there are no standardised protocols for TWO_2. So, randomised control studies are needed to increase the evidence around the use and effectiveness of TWO_2 therapy and to establish optimal parameters for use.

DOI: 10.1530/endoabs.37.EP504

EP505

The use of insulin pump therapy in the paediatric age group

Hanna Mikhno[1], Angelica Solntsava[2] & Natalia Volkova[2]
[1]2nd City Children's Hospital, Minsk, Belarus; [2]Belarusian State Medical University, Minsk, Belarus.

The use insulin pump therapy (IPT) (continuous subcutaneous insulin infusion (CSII)) has increased dramatically in youth with type 1 diabetes (T1D) in the past decade.
Objective
Rate metabolic compensation of diabetes mellitus in children on IPT on the level HbA1c and self-control of glycaemia.
Methods
The examination of 19 children aged 12.55 ± 3.75 years (boys/girls = 13/6), with T1D, observed in '2nd City Children's Hospital' in Minsk. Up to IPT patients were on basal-bolus insulin therapy. Patients transferred to the IPT because of frequent uncontrolled hypoglycaemia. Evaluated the dose of insulin per kilogram body weight, blood glucose self-monitoring during the day, the presence of ketoacidosis, hypoglycaemic and hyperglycaemic conditions, the level of HbA1c.
Results
100% of the patients complained of unstable blood glucose levels throughout the day. Clinical manifestation of diabetes observed in age 6.83 ± 3.72 years. Longevity of diabetes this patients was from 0.5 to 16 years (4.91 ± 4.10 years). Insulin dose per kilogram body weight on a basis of bolus insulin was 0.88 ± 0.40 U/kg. HbA1c was 7.30 ± 0.86%. Hypoglycaemic coma was in two children (10.53%). Self-monitoring of blood glucose was performed 8.9 ± 3.6 times a day. Term of use pump 1.31 ± 1.15 years. Five patients were in the ICU for more than 1 year (2.49 ± 1.02 years). The IPT insulin dose per kilogram of body weight was 0.90 ± 0.29 U/kg ($P=0.005$), HbA1c was 6.49 ± 0.74% ($P=0.002$). Self-monitoring of blood glucose for IPT 7.15 ± 2.89 times a day. IPT is not mentioned on the hypoglycaemic, severe hypoglycaemia, ketoacidosis, and hyperglycaemic conditions. The frequency change modes basal insulin dose during the day 4.8 ± 1.5 times.
Conclusions
Children who are on insulin pump therapy during the year was a significant reduction in HbA1c at 11.10% ($P=0.002$), indicating that the long-term metabolic compensation in all age groups.

DOI: 10.1530/endoabs.37.EP505

EP506

Relation between psychiatric symptoms and diabetic complications: preliminary results

Dilek Tuzun[1], Emine Duygu Ersozlu Bozkirli[2], Ayten Oguz[1], Murat Sahin[1], Tugba Yilmaz[3], Berivan Ganidagli[3], Omer Faruk Akgul[3] & Kamile Gul[1]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey; [2]Division of Rheumatology, Adana Numune Training and Research Hospital, Adana, Turkey; [3]Department of Internal Medicine, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey.

Aim
In this study, we aimed to assess psychiatric symptoms in 1000 type 2 diabetes mellitus (T2DM) patients.
Material and methods
297 patients (mean age 52.13±9.37 years, 190 women and 107 men) who had T2DM were included as a preliminary in this study. The presence of cheiroarthropathy, Dupuytren's contracture, tinnel sign, and tendinitis was assessed. Diabetic retinopathy was assessed by direct ophthalmoscopy. Urinary albumin excretion was determined in at least two 24 h urine samples. Beck's Depression Inventory (BDI) and Beck's Anxiety Inventory (BAI) were administered.
Results
The mean diabetic duration was 7.71±6.28 years. Dupuytren's contracture was present in 7.7%, cheiroarthropathy in 11.1%, tinnel sign in 19.5%, and tendinitis in 4.4%. Retinopathy was present in 15.5%, nephropathy in 18.2%. BDI score was 13.92±9.93 and BAI score was 16.89±13.63. There was positive correlation between BDI score and diabetic nephropathy ($P=0.001$, $r=197$). Also, there was positive correlation between BDI score and tinnel sign ($P=0.000$, $r=241$). Positive correlation between BAI score and diabetic nephropathy was detected ($P=0.019$, $r=136$). There was positive correlation between BAI score and tinnel sign ($P=0.00$, $r=232$). The suggested BDI cutoff of ≥ 17 had 81% sensitivity and 79% specificity and classified as clinically depressed. In our study BDI score ≥ 17 was 33.3%. BAI score ≥ 17 was classified as moderate and serious anxious. In our study BAI score ≥ 17 was 40.4%.
Conclusions
Psychiatric symptoms, especially depression and anxiety, are widely seen in patients with diabetes mellitus. Quality of life and disability are correlated with depression and anxiety levels. Therefore, in addition to the recent management of DM, psychiatric symptoms such as depressed mood and anxiety should also be taken into consideration in order to increase the quality of life in DM patients.

DOI: 10.1530/endoabs.37.EP506

EP507

The diabetic hand: a forgotten complication?

Dilek Tuzun[1], Emine Duygu Ersozlu Bozkirli[2], Ayten Oguz[1], Murat Sahin[1], Irem Sahin[3], Hakan Demir[3], Elif Inanc[3], Berivan Ganidagli[3] & Kamile Gul[1]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey; [2]Division of Rheumatology, Adana Numune Training and Research Hospital, Adana, Turkey; [3]Department of Internal Medicine, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey.

Aim
Diabetes mellitus is a chronic metabolic condition characterised by persistent hyperglycaemia with resultant morbidity and mortality related primarily to its associated microvascular and macrovascular complications In this study our aim was to investigate the prevalence of the most frequently occurring hand complications in 1000 type 2 diabetes mellitus (T2DM) patients.
Material and methods
297 patients (mean age 52.13±9.37 years, 190 women and 107 men) who had T2DM were included as a preliminary in this study. The presence of cheiroarthropathy, Dupuytren's contracture, tinnel sign, and tendinitis was assessed. All patients were evaluated also by the Rheumatology Division. Diabetic retinopathy was assessed by direct ophthalmoscopy. Urinary albumin excretion was determined in at least two 24 h urine samples.
Results
The mean diabetic duration was 7.71±6.28 years. Dupuytren's contracture was present in 7.7%, cheiroarthropathy in 11.1%, tinnel sign in 19.5%, and tendinitis in 4.4%. Retinopathy was present in 15.5% and nephropathy in 18.2%. Mean HbA1c was 8.58±2.03. Mean fasting glucose was 174.6±69.22 mg/dl. The relationship between these complications and patients' age, sex, duration of diabetes, and glycaemic control was also analysed. There was positive correlation between age and cheiroarthropathy and dupuytren's contracture ($P=0.01$, $r=193$ and $P=0.000$, $r=248$ respectively). There was positive correlation between diabetic duration and diabetic retinopathy ($P=0.000$, $r=216$). There was positive correlation between diabetic duration and cheiroarthropathy ($P=0.044$, $r=117$). There was positive correlation between diabetic nephropathy and tinnel sign ($P=0.005$, $r=164$).
Conclusions
Some musculoskeletal disorders are more prevalent in T2DM patients and this may be associated with duration of diabetes. Also the hand abnormalities were associated with the diabetic complications. Long-term prospective randomised controlled trials on preventing musculoskeletal complications and disability in diabetics are needed.

DOI: 10.1530/endoabs.37.EP507

EP508

Moderate and severe hypoglycaemia associated metabolic changes in cortex and hippocampus of mice

Vigneshwaran Pitchaimani
Niigata University of Pharmacy and Applied Life Sciences, Niigata, Japan.

Objective
It is common in the clinical setting that the reperfusion of glucose after severe hypoglycaemia. Starvation leads to decrease in blood glucose level (BGL) and this shifts the brain to utilize less glucose and utilize other alternative fuels. This led us investigate how the brain decreases the glucose uptake during starvation and how it utilizes the glucose under severe hypoglycaemia.
Results
To understand the mechanism we checked the neuronal glut3, glut1 in expression by western blot analysis in the cortex and hippocampus in 24 h fasted and 2 IU/kg insulin induced hypoglycaemia mice at different intervals (10, 30, and 90 min). Our results suggesting that 24 h fasting significantly decreases the BGL (58± 2 mg/dl) from fed mice BGL (120.3±6) and it slightly decreases the glut3 in cortex and hippocampus. In the insulin induced hypoglycaemia group, the BGL of 10 min after was (67.8 mg/dl), 30 min after was (54.80 mg/dl) and 90 min after was below (20 mg/dl). The glut3 expression in the 10 min was not altered but the 30 min after insulin administration decreases the glut3 more but not significant, whereas the glut3 in the 90 min after was restored to normal level. No change in the expression glut1 was observed.
Conclusion
The decreased BGL at the range nearly of 60 mg/dl during fasting or insulin induced hypoglycaemia, the neuron may utilize less glucose (decreased glut3) and may prefer astrocyte lactate (no change in glut1) and other fuel for metabolism. The decreased BGL below 20 mg/dl, the neuron may try to utilize the glucose directly (restored glut3) and from astrocytes (no change in glut1) and also from other fuels to restore the normal metabolism.
Disclosure
This research was supported by Ministry of Education, Culture, Sports, Science and Technology, Japan, and by a grant from the promotion and mutual aid corporation for Private schools, Japan (23602012 and 26460239) respectively.

DOI: 10.1530/endoabs.37.EP508

EP509

Diabetes mellitus and chronic kidney disease: two decades of consultation of diabetes and kidney transplant, a retrospective study

Ana Margarida Balsa[1], Margarida Bastos[2], Rosa Dantas[1], Carla Batista[2], Rui Alves[3], António Roseiro[3], Carolina Moreno[2], Daniela Guelho[2], Luís Cardoso[2], Nuno Vicente[2], Diana Martins[2], Diana Oliveira[2], Márcia Alves[1], Joana Guimarães[1], Alfredo Mota[4] & Francisco Carrilho[2]
[1]Serviço de Endocrinologia, Diabetes e Nutrição do Centro Hospitalar do Baixo Vouga, Aveiro, Portugal; [2]Serviço de Endocrinologia, Diabetes e Metabolismo do Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; [3]Serviço de Nefrologia do Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; [4]Serviço de Urologia e Transplantação Renal do Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.

Introduction
Diabetic nephropathy is the main global cause of end stage renal disease. According to the annual report from the Portuguese National Diabetes Observatory, in 2013, the prevalence of diabetes mellitus (DM) in new cases of chronic kidney disease was 31.2 and 11.1% in kidney transplant patients.
Aim
To characterise the population of type 2 diabetic patients admitted in diabetes and kidney transplant consult (DKTC), comparing those admitted between the decades of Jan 1992–Dec 2001 (D1) and Jan 2002–Dec 2011 (D2).
Methods
Retrospective analysis of 238 out of 332 patients admitted in DKTC (D1, $n=66$ and D2, $n=172$); the registered data included age, sex, weight, BMI, age of diagnosis, duration of DM and therapeutic, metabolic control, macro and microvascular complications at first admission. Statistical analysis was performed with SPSS.
Results
D1 patients had an average age at of 56.91 ± 7.75 and 15.36 ± 8.29 years of DM and a HbA1c of $7.56\pm1.83\%$. 68.2% of patients D1 had retinopathy (51.5% proliferative); 31.8% had neuropathy; 7.6% had been submitted to amputation (6.1% minor and 1.5% major); 36.4% presented macrovascular complications. 33.8% completed the selection process and were transplanted. D2 patients had an average age of 59.46 ± 7.08 and 15.76 ± 8.61 years of DM and a HbA1c of $7.13\pm1.47\%$. Retinopathy was present in 65.1% of D2 patients (43.1% proliferative); neuropathy in 33.1%; 8.8% had been submitted to amputation (5.9% minor and 2.9% major); 27.2% had macrovascular complications. 32.1% D2 patients were transplanted. D2 patients were older than D1 ($P=0.016$) but had a lower prevalence of cardiac ischemic disease ($P=0.007$). No other statistical significant differences were found between the two decades.
Conclusion
Diabetic patients admitted in DKTC generally have a long evolution of DM, with several co-morbidities and complications. Even though in the last decade more and older DM2 patients were referred to kidney transplantation, we did not find an increase in those patient's complications.

DOI: 10.1530/endoabs.37.EP509

EP510

Study of irisin hormone level in type 2 diabetic patients and patients with diabetic nephropathy

Salah Shelbaya, Manal Abushady, Merhan Samy, Yasmin Abd El Mageed & Magdy Abbas
Ain Shams University, Cairo, Egypt.

Background
Chronic kidney disease secondary to type 2 diabetes is associated with multifactorial energy dysmetabolism. Irisin has been identified recently as an exercise induced hormone secreted by skeletal muscles. It is hypothesised that patients with CKD may have altered irisin levels.
Aim of the work
We aimed to study irisin hormone in type 2 diabetic patient and to assess its relation with diabetic nephropathy (DN).
Subjects and methods
We recruited 60 type 2 diabetic subjects and 30 healthy controls. Diabetics will be divided into 30 patients without complications and 30 with DN. Serum irisin, fasting blood glucose (FBG), 2 h plasma glucose (2 h PG), HbA1c, serum creatinine, and albumin/creatinine ratio were measured.
Results
Irisin was significantly decreased in type 2 diabetic patients compared to control (34.46 ± 15.28 ng/ml vs 152.600 ± 39.581 ng/ml, $P<0.001$). Patients with DN had lower irisin than diabetics without complications (20.967 ± 4.476 ng/ml vs 47.967 ± 8.853 ng/ml, $P<0.01$). There was a significant negative correlation between irisin and systolic blood pressure ($r=-0.493$), diastolic blood pressure ($r=-0.625$), serum creatinine ($r=-0.729$), duration of diabetes ($r=-0.942$), albumin/creatinine ratio ($r=-0.696$), BMI ($r=-0.396$), and HbA1c ($r=-0.305$) in all diabetic patients.($P<0.05$). Multivariant regression analysis showed that duration of diabetes is the only independent determinant for irisin level.
Conclusion
There is a decrease in serum irisin level in patients with type 2 diabetes and a further significant decrease in patients with DN.

DOI: 10.1530/endoabs.37.EP510

EP511

A puzzling bilateral diabetic foot problem

Nathalie Denecker, Dimitri Aerden & Michel De Maeseneer
UZ Brussel, Brussels, Belgium.

Introduction
Charcot neuroartropathy (CN) is a devastating complication of diabetes rapidly leading to irreversible foot deformity when misdiagnosed. Differential diagnosis with foot infections and other foot-related diseases remains challenging.
Case
A 58-year-old woman with type 2 diabetes was hospitalised with a red, swollen left leg and high fever. The diagnosis of erysipelas with a neuropathic wound of the first digit as the entry wound was established. After antibiotic treatment, the infection abated and the patient was discharged. Twelve days later she visited the Emergency Department with increased swelling and pain of the left leg, residual redness and a new skin defect on the left second toe. Ten days later, she was seen at the diabetic foot clinic. The patient reported a recent trauma, which had resulted in pain and a swollen, red right foot. X-rays and a bone scintigraphy with SPECT–CT were performed and surprisingly suggested CN of both feet, a finding that was later confirmed by MRI. A clinically suspected osteomyelitis of the left second digit was ruled out with a leucocyte scan and SPECT–CT. Immobilisation for 3 months with bilateral total contact casts (TCC) was deemed impracticable, so the left foot was treated with an aircast walker instead. Clinically the inflammatory signs subsided but bilateral talar oedema remained noticeable on MRI. Bilateral aircast walkers were advised for another 2 months until custom-made shoes became available.
Conclusion
The diagnosis of an active Charcot foot remains challenging, especially after previous infection or trauma which both may trigger CN. Bilateral CN, although extremely rare, further complicates early diagnosis and efficient bilateral offloading.

DOI: 10.1530/endoabs.37.EP511

EP512

Continuous subcutaneous insulin infusion decreases hypoglycaemia during nighttime

Nuno Vicente, Luís Cardoso, Carla Baptista, Luísa Barros, Daniela Guelho, Diana Oliveira, Diana Martins & Francisco Carrilho
Serviço de Endocrinologia, Diabetes e Metabolismo, Centro Hospitalar Universitário de Coimbra, EPE, Coimbra, Portugal.

Introduction
Continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI) are forms of intensified insulin therapy and the most used regimens for type 1 diabetes (T1D). Owing to its continuous basal output, hypoglycaemic events tend to be rarer with CSII. Our goal was to evaluate the differences in nocturnal hypoglycemia between these two treatment strategies.
Methods
Retrospective analysis of 61 patients who had performed continuous glucose monitoring (Ipro2, Medtronic, Northridge, CA, USA). All patients had T1D and were either on CSII or MDI. Hypoglycaemia was defined as glucose level <70 mg/dl. Daytime (DT) was defined as the period from 0700 to 2300 h and nighttime (NT) was from 2300 to 0700 h.
Results
We obtained 112 714 glucose measurements (42 132 on CSII and 70 582 on MDI). Our sample had mean age of 31.7 ± 8.8 years, BMI of 22.7 ± 7.5 kg/m^2 and a mean glucose of 156 ± 73 mg/dl. Those on CSII were older (33.0 years vs 31.2 years, $P<0.05$), heavier (25.7 kg/m^2 vs 20.8 kg/m^2, $P<0.05$), had a more prolonged duration of T1D (19.4 years vs 16.4 years, $P<0.05$) and a higher mean glucose measurement (162 mg/dl vs 154 mg/dl, $P<0.05$) than those on MDI. Hypoglycaemia was more frequent in the MDI group (7410 vs 2608 measurements, $P<0.05$) and mean HbA1c was similar (7.9 vs 8.0, $P>0.05$). Hypoglycaemia was more frequent in the MDI group, especially during NT ($P<0.05$ for both).
Conclusion
Despite similar HbA1c in the two groups, hypoglycaemia is more frequent in the MDI group, particularly at NT period.

DOI: 10.1530/endoabs.37.EP512

EP513

Insulin prescription audit

Nabeel Saeed[1,2] & Mary Jane Brassill[1]
[1]South Tipperary General Hospital, Clonmel, Ireland; [2]Queen Elizabeth Hospital, Kingslynn, UK.

Insulin is a life-saving drug but can be life threatening if not prescribed properly. A prospective, consecutive audit of insulin prescription was carried out on all medical and surgical patients admitted to South Tipperary General Hospital with types 1 and 2 diabetes mellitus in November 2013. The practice was compared with hospital guidelines which are consistent with other hospitals nationally. Three prescribing practices were audited: i) the prescription of insulin on insulin prescription sheets (as per hospital policy) or drug kardex; ii) the adjustment of insulin doses on insulin prescription sheets as per blood sugar levels; and iii) the prescription of insulin on discharge prescription. Twenty consecutive patients were audited. 65% had insulin charted on insulin prescription sheet, 15% on drug kardex alone and 20% on both. 80% of patients had their insulin dosage corrected as per blood glucose readings on insulin prescription sheet, 10% on both and 10% did not need insulin dose correction. 60% of patients had insulin prescribed on discharge prescription whereas 40% did not and the reasons for this were analysed. As a result of these findings a new insulin prescription sheet was recommended and introduced with regular and supplementary insulin sections. Educational sessions on insulin prescription were also organised. A re-audit of a further twenty patients was performed in June 2014 to look at the above three prescribing practices. It showed 100% compliance in terms of insulin prescription. 90% compliance was observed in terms of insulin dose adjustment as per blood glucose readings. The remaining 10% did not require correction of insulin dose. 65% of patients had insulin prescribed on discharge, 10% did not require insulin on discharge, 10% died and 15% were still inpatients at time of re-audit. The re-audit showed an improvement in the practice of insulin prescribing and therefore improved patient safety.

DOI: 10.1530/endoabs.37.EP513

EP514

Distribution of fat mass in young type 1 diabetic patients

Yulia Dydyshko & Alla Shepelkevich
Belarusian State Medical University, Minsk, Belarus.

Background
There is convincing evidence that the increasing of visceral fat is a risk factor for vascular disease. Type 1 diabetes mellitus (T1DM) is characterized by the development of micro-, and later, and macrovascular complications. The aim of the study was to examine features of body composition fat distribution parameters in T1DM patients.
Materials and methods
96 patients with T1DM (59 women and 37 men) (mean age: 32.52±10.71 years, duration of DM: 12 (7.5–20) years, age of manifestation: 18 (13–23.5) years), BMI: 23.47±3.16, HbA1c: 8.45±1.2% and 54 (30 women and 24 men) controls matched for age, sex, and BMI were examined. Body composition was determined by dual energy X-ray absorptiometry.
Results
Fat mass parameters in T1DM males and controls males were: android fat: 27.41±11.43% vs 28.8±9.67% ($P=0.627$); gynoid fat: 28.06±7.15% vs 26.74±7.74% ($P=0.506$); A/G ratio: 0.95±0.24 vs 1.06±0.15 ($P=0.048$); total body: 23.02±7.9% vs 22.55±7.5% ($P=0.819$); trunk/total: 0.516±0.07 vs 0.54±0.034 ($P=0.094$); legs/total: 0.35±0.06 vs 0.32±0.032 ($P=0.093$); and (arms+legs)/trunk: 0.9±0.28 vs 0.77±0.105 ($P=0.034$). Similar features in T1DM women and controls women were: android fat: 32.29±8.44% vs 32.37±10.81% ($P=0.97$); gynoid fat: 41.72±6.63% vs 41.36±7.16% ($P=0.81$); A/G ratio: 0.76±0.14 vs 0.45±0.05 ($P=0.97$); total body: 33.25±6.7% vs 32.3±7.59 g ($P=0.551$); trunk/total: 0.44±0.048 vs 0.45±0.056 ($P=0.611$); legs/total: 0.412±0.05 vs 0.415±0.054 ($P=0.812$); and (arms±legs)/trunk: 1.18±0.25 vs 1.17±0.3 ($P=0.837$). Gynoid (peripheric) fat distribution was positively correlated with the age of T1DM males ($r=0.19$; $P=0.018$), however no correlation was found with the duration of the disease, level HbA1c, the total daily insulin dose.
Conclusions
The peripheral type of fat mass distribution is dominated at T1DM males compared with control, while there were no differences in the distribution of adipose tissue among the investigated women. The obtained data indicate gender differences in the distribution of fat mass in T1DM patients.

DOI: 10.1530/endoabs.37.EP514

EP515

Roux-en-Y gastric bypass reduces proteinuria in diabetic kidney disease to a greater extent than weight loss alone in the Zucker diabetic fatty rat without a greater improvement in renal inflammation

Karl Neff[1], Jessie Elliott[1], Sabrina Jackson[1], Kathrin Abegg[2,3], Caroline Corteville[2,3], Rodrigo Munoz[4], Neil Docherty[1], Thomas Lutz[2,3] & Carel le Roux[1]
[1]School of Medicine and Medical Sciences, Conway Institute, Diabetes Complications Research Centre, University College Dublin, Dublin, Ireland; [2]Vetsuisse Faculty, Institute of Veterinary Physiology, University of Zurich, Zurich, Switzerland; [3]Institute of Laboratory Animal Sciences, University of Zurich, Zurich, Switzerland; [4]Department of Digestive Surgery, School of Medicine Santiago, Pontificia Universidad Católica, Santiago, Chile.

Background
The effect of Roux-en-Y gastric bypass (RYGB) on diabetic kidney disease (DKD) is unclear. We used a Zucker diabetic fatty rat (ZDF) model of DKD to determine the effect of RYGB on histopathological markers of DKD, proteinuria, and MCP1 excretion.
Methods
ZDF rats underwent RYGB ($n=15$) or sham surgery ($n=14$) at 18 weeks of age. Eight sham operated animals were food restricted to match the weight loss of the RYGB group (body-weight matched (BWM) group). Animals were sacrificed at age 31 weeks.
Results
Macrophage infiltration (ED1 staining), urinary MCP1:creatinine ratio and MCP1 expression was reduced by in both RYGB and BWM groups ($P<0.05$). Despite similar effects on inflammation, RYGB had a greater effect on reducing proteinuria ($P=0.01$).
Conclusions
Weight loss alone can remediate renal inflammation, but RYGB has a greater effect on proteinuria. This may be due to other mechanisms such as incretin effects.
Disclosure
This work was supported by Science Foundation Ireland ref 12/YI/B2480.

DOI: 10.1530/endoabs.37.EP515

EP516

Assessment of the myelin damage degree in patients with and without diabetic neuropathy

Iryna Kostitska
Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine.

Background and aims
Diabetic neuropathy is associated with impaired neuron myelination, nerve conduction, and muscle function. The pathogenic mechanisms of reduced myelination in diabetes mellitus are poorly understood. Peripheral myelin protein 22 (PMP22) is glycoprotein with proposed roles in peripheral nerve myelin formation. This study allows us to consider the changes in the plasma levels of PMP22 in patients with and without diabetic neuropathy.
Materials and methods
We studied 34 subjects with DM duration of 15.2±2.1 years, mean value of HbA1c was 8.4±1.2% divided into two groups: diabetic patients without symptoms of peripheral somatic neuropathy (PSN) (consisted of 12 participants (five males/seven females), mean age was 42.7±10.1 years) and patients with diabetes and confirmed diagnosis of diabetic PSN (22 patients (eight males/14 females), mean age was 42.8±10.1 years) and 20 healthy volunteers (nine males/11 females, mean age was 48.3±9.5 years) as the control group. The plasma concentrations of PMP22 were measured by immunoassay. No subjects studied had signs of other disorders of peripheral nervous system.
Results
We found that plasma levels of PMP22 were significantly higher in the patients with PSN (9.1±1.32 ng/ml) compared to diabetic subjects without PSN (3.8±0.15 ng/ml) and control group (1.53±0.31 ng/ml), $P<0.05$.
Conclusion
These findings could suggest the occurrence of the neuron demyelination reflected by the elevated PMP22 in patients with diabetic neuropathy.

DOI: 10.1530/endoabs.37.EP516

EP517

Tear function tests in pregnant women with gestational diabetes mellitus

Seyfullah Kan[1], Ugur Acar[2,5], Muhammed Kizilgul[3], Emrullah Beyazyildiz[4], Ali Bulent Cankaya[2], Mahmut Apaydin[3], Selvihan Beysel[3], Mustafa Ozbek[3] & Tuncay Delibasi[3]
[1]Department of Endocrinology and Metabolism, Ankara Teaching and Research Hospital, Ankara, Turkey; [2]Department of Ophthalmology, Faculty of Medicine, Hacettepe University, Ankara, Turkey; [3]Department of Endocrinology and Metabolism, Diskapi Teaching and Research Hospital, Ankara, Turkey; [4]Department of Ophthalmology, Samsun Teaching and Research Hospital, Samsun, Turkey; [5]Department of Internal Medicine, School of Medicine (Kastamonu), Hacettepe University, Kastamonu, Turkey.

Aim
Gestational diabetes mellitus (GDM) is a disorder which is described as impaired glucose tolerance which firstly occurs first time during pregnancy. We aimed to evaluate the tear function tests such as Schirmer, tear break-up time (TBUT), tear film osmolarity (TFO), and ocular surface disease index (OSDI) score in pregnant with GDM.
Methods
Pregnant women with GDM and healthy pregnant who were matched in both age and gestational age were enrolled into the study. The women with ocular or systemic disorders that may affect the tear function tests, and who use topical medications were excluded from the study. All of the pregnant answered the OSDI questionnaire, afterwards they underwent a detailed ophthalmic examination including Schirmer, TBUT, and TFO by the same ophthalmologist.
Results
Forty-six pregnant with GDM whose mean age of 30.43 ± 4.75 years and 36 healthy pregnant whose mean age of 28.83 ± 4.42 years were enrolled into the study. The mean gestational ages were 25.80 ± 1.61 and 26.19 ± 1.43 weeks respectively. There were not statistically significant differences between two groups in terms of age and gestational age. The mean fast blood glucose and the mean HbA1c levels were statistically significantly higher ($P < 0.001$, for each) in GDM group (105.17 ± 7.28 mg/ml and $5.57 \pm 0.50\%$) compared to healthy group (70.17 ± 6.54 mg/ml and $4.93 \pm 0.29\%$). The levels of Schirmer test, TBUT test, TFO, and OSDI score were 11.20 ± 4.93 mm, 5.59 ± 2.16 s, 309.65 ± 14.80 mOsm/l and 9.59 ± 9.69 points in GDM group, and 12.33 ± 5.33 mm, 5.67 ± 2.68 s, 308.36 ± 16.00 mOsm/l and 10.62 ± 8.66 points in healthy group. There were not statistically significant difference in any of the tear function tests between two groups.
Conclusions
To the best of our knowledge, there is no study in the literature about the effects of GDM on dry eye parameters. Although, GDM cause many negative consequences on pregnant women, it seems to be no negative effects on tear function tests.

DOI: 10.1530/endoabs.37.EP517

EP518

The impact of non-alcoholic fatty liver disease on carotid artery intima–media thickness as a risk factor for atherosclerosis

Cristina Alina Silaghi[1,2], Anca Elena Craciun[2], Daniel Tudor Cosma[2], Horatiu Silaghi[2], Romina Negru[2], Cristina Feurdean[2], Andrada Oltean[2], Nicolae Hancu[2] & Carmen Georgescu[2]
[1]County Clinic Emergency Hospital Cluj, Cluj, Romania; [2]'Iuliu Hatieganu' University of Medicine and Pharmacy Cluj-Napoca, Cluj, Romania.

Introduction
Non-alcoholic fatty liver disease (NAFLD) is considered a hepatic manifestation of metabolic syndrome and is closely associated with abdominal obesity, atherogenic dyslipidaemia, and diabetes exposing subjects with NAFLD to an increased risk of developing cardiovascular disease. The aim of this study is to determine the prevalence of NAFLD in diabetes mellitus (DM) patients, to correlate it to the subclinical atherosclerosis in these patients.
Description of method
One hundred and twenty-four consecutive patients with type 2 DM were enrolled. NAFLD was diagnosed using fatty liver index (FLI), an algorithm based on BMI, waist circumference, triglycerides, and gamma glutamyl-transferase (GGT). Carotid atherosclerosis (intima–media thickness (IMT)) was evaluated by high-resolution carotid B-mode ultrasonography. Plasma liver function tests and other biochemical blood measurements were determined.
Results
Patients were divided into three groups: G1: FLI < 30 ($n = 56$); G3: FLI > 60 ($n = 40$); and G2: intermediate group ($n = 28$). The prevalence of NAFLD using FLI ≥ 60 in DM patients was 40 patients (32%). CIMT increased with FLI (G3 = 0.54 ± 0.08 mm vs G1 = 0.40 ± 0.08 mm, $P < 0.0001$). FLI was associated with increased LDL cholesterol ($r = 0.38$), alanine aminotransferase ($r = 0.55$), BMI ($r = 0.34$), diastolic blood pressure ($r = 0.41$) and triglycerides ($r = 0.49$), and reduced HDL cholesterol ($r = -0.52$) and insulinaemia ($r = -0.30$, all $P < 0.0001$). The correlations hold also in multivariate analysis after adjusting for age and gender. Behavioural variables (smoking and diet) and fasting plasma glucose, did not significantly differ between subjects with and without FLI.
Conclusion
NAFLD increases the risk of subclinical atherosclerosis in DZ patients. DM patients with NAFLD in our study showed significant correlation with cardiovascular risk factors.
Disclosure
European Social Found, Houman Resources Development Operational Programme 2007–2013, projet no. POSDRU/159/1.5/138776.

DOI: 10.1530/endoabs.37.EP518

EP519

Self-monitoring of blood glucose patterns among Turkish diabetic patients

Kevser Onbasi, Turkan Pasali Kilit & Orcun Kuet
Dumlupinar University, Kutahya, Turkey.

Self-monitoring of blood glucose (SMBG) increases life expectancy and improves diabetic patients' quality of life. 17 type 1 diabetic patients and 159 type 2 diabetic patients' files were randomly evaluated to evaluate SMBG practice patterns in our hospital. All type 1 patients used insulin, while 38 type 2 diabetic patients used drug only, 35 type 2 diabetic patients used drugs in combination with insulin and 86 type 2 diabetic patients used insulin only. 90.3% of our patients owned a glucometer. Although, this high percentage one of the type 1 and nine of the type 2 diabetic patients did not practice SMBG despite owning a glucometer. 23.5% of type 1 diabetic patients and 47.2% of type 2 diabetic patients only measured their fasting glucose levels. 11.8% of type 1 diabetic patients and 4.4% of type 2 diabetic patients only measured their postprandial glucose levels. 58.8% of type 1 diabetic patients and 40.9% of type 2 diabetic patients measured fasting and postprandial glucose levels. Only a minority (33.3%) of those using insulin practiced daily SMBG. Seven patients of those using insulin did not practice SMBG. 31 patients reported to examine their blood glucose levels if they were symptomatic. 20 patients monitored their blood glucose weekly, three patients once monthly and 15 every second day. Seven patients checked their blood glucose level twice daily, three patients three times, five patients four times, and one patient checked their blood glucose levels six times daily. Adjusting the insulin dose according to SMBG levels is performed only in 39.1% of patients. 84 patients do not make an adjustment of the insulin dose despite performing SMBG. 56 patients did never check postprandial glucose levels. In summary the majority of our patients does not perform SMBG levels adequately and do not adjust their medicament doses or insulin doses.

DOI: 10.1530/endoabs.37.EP519

EP520

New-onset diabetes after renal transplantation (NODAT) and nodular glomerulosclerosis of the renal allograft

Diana Martins[1], Carla Baptista[1], Margarida Bastos[1], Jorge Pratas[2], Rui Alves[2], Catarina Romãozinho[2], Carol Marinho[3], Joana Saraiva[1], Carolina Moreno[1], Daniela Guelho[1], Nuno Vicente[1], Luís Cardoso[1], Margarida Balsa[4], Diana Oliveira[1], Alfredo Mota[5] & Francisco Carrilho[1]
[1]Endocrinology, Diabetes and Metabolism Department, Coimbra Hospital and University Centre, Coimbra, Portugal; [2]Nephrology Department, Coimbra Hospital and University Centre, Coimbra, Portugal; [3]Pathological Anatomy Department, Coimbra Hospital and University Centre, Coimbra, Portugal; [4]Endocrinology, Diabetes and Nutrition Department, Baixo Vouga Hospital Centre, Aveiro, Portugal; [5]Urology and Renal Transplantation Department, Coimbra Hospital and University Centre, Coimbra, Portugal.

Introduction
Diabetes mellitus is a common metabolic complication after kidney transplantation, occurring with a frequency of 15–30% in the first year. However, despite the high incidence, there are described few cases of diabetic nephropathy with nodular glomerulosclerosis of the allograft.
Case
Female patient, 49, with autosomal dominant familial renal poliquistose diagnosed at 17 and progression for chronic end-stage renal disease, underwent renal transplantation of cadaver in June 2004. Five months after transplant and having started immunosuppressive therapy with tacrolimus, sirolimus, and prednisone, was diagnosed with diabetes mellitus. Initiated conventional intensive insulin therapy, with gradual decrease of the total daily dose after suspension of prednisone and reduction of the remaining immunosuppressants.
Instead of maintaining an optimized glycaemic control (HbA1c $<7\%$), it was found chronic renal allograft dysfunction, 9 years and 5 months after transplantation, the patient had marked reduction of glomerular filtration rate (<20 ml/min) with proteinuria in nephrotic range. Graft biopsy was performed and histopathological and immunohistochemical evaluation demonstrated 'nodular glomerulosclerosis in diabetes mellitus context, without acute rejection, with observed mild chronic rejection phenomena with mild tubular atrophy and fibrosis'. In April 2014, the patient kept worsening glomerular filtration rate of $\sim$15 ml/min per 1.73 m^2 and an HbA1c of 6.6%, under exclusive immunosuppression with tacrolimus.
Conclusions
In the case described, there was progressive graft dysfunction despite good glycemic control, with confirmed nodular glomerulosclerosis typical lesions. Thus, in the NODAT with renal allograft dysfunction, it is not excluded the possibility of association with diabetic nephropathy. This case also shows that in NODAT there are the same risk factors for the occurrence of late diabetic complications.

DOI: 10.1530/endoabs.37.EP520

EP521

Sexual functioning and distress in types 1 and 2 diabetic women: a two-centres experience

Konstantinos Dimitropoulos[1], Vassilios Tzortzis[1], Agathi Vassiliou[2], Eleftheria Mparmpa[2], Magdalini Mpristianou[3] & Alexandra Bargiota[2]
[1]Department of Urology, Faculty of Medicine, University of Thessaly, Larissa, Thessaly, Greece; [2]Department of Endocrinology and Metabolic Diseases, Faculty of Medicine, University of Thessaly, Larissa, Thessaly, Greece; [3]Department of Internal Medicine, General Hospital of Lamia, Lamia, Greece.

Introduction
A high prevalence of sexual disorders has been observed in women with types 1 and 2 diabetes mellitus (DM). Here we present 4 years, two-center results of the study of disorders of female sexual functioning in female patients with diabetes.
Materials and methods
During the time period 2011–2014, female DM patients and healthy controls were enrolled according to the protocol inclusion criteria. The FSFI, FSDS, and GHQ-28 questionnaires were used to evaluate sexual functioning, sexual distress, and general health respectively. Comparative and regression tests were used to analyse data.
Results
In total, 221 patients and 218 healthy controls were enrolled. Of the 221 patients, 107 (48.4%) had a diagnosis of T1DM and the remaining 114 (51.6%) had T2DM. Control group was divided to CG-1 and CG-2 (104 and 114 women respectively) subgroups, each one age matched for T1DM and T2DM subgroups.
Diabetic patients in general, had significantly lower FSFI and higher FSDS scores compared to the healthy controls ($P<0.05$). T1DM and T2DM women also had significantly lower FSFI and higher FSDS scores compared to CG-1 and CG-2 controls ($P<0.05$).
Diagnosis of 'any' diabetes, was found to be a significant predictor of FSD (OR 2.746, $P<0.05$). T1DM and T2DM women were 2.698 and 2.887 times more likely to have FSD compared to CG-1 and CG-2 non patients respectively ($P<0.05$). Psychosocial factors, mainly depression, were found to be significant determinants for FSD in diabetic and non diabetic women ($P<0.05$).
Conclusion
The current study findings confirm that FSD is more prevalent in women with diabetes. Both types of diabetes were found to be significant determinants for FSD in the patients of our study. Moreover, the role of psychosocial factors, such as depression, in the pathogenesis of sexual disorders and distress in both diabetic and non-diabetic women is highlighted.

DOI: 10.1530/endoabs.37.EP521

EP522

Association of SNPs in the intergenic region of OCT2 and OCT3 with short-term efficiency of metformin monotherapy in the type 2 diabetes patients

Janis Klovins[1], Linda Zaharenko[1], Kristine Geldnere[2], Ilze Konrade[5], Solveiga Grinberga[4], Osvalds Pugovics[4], Ineta Kalnina[1] & Valdis Pirags[2,3]
[1]Latvian Biomedical Research and Study Centre, Ratsupites 1, LV1067 Riga, Latvia; [2]Department of Endocrinology, Pauls Stradins Clinical University Hospital, Pilsonu Str. 13, LV1002 Riga, Latvia; [3]Faculty of Medicine, University of Latvia, Sarlotes Str. 1a, LV1001 Riga, Latvia; [4]Latvian Institute of Organic Synthesis, Riga, Latvia; [5]Department of Medicine, Riga East Clinical University Hospital, Riga Stradins University, Riga, Latvia.

Clinical response to metformin is highly variable in type 2 diabetes (T2D) patients highlighting the need for identification of genetic components affecting the efficiency of metformin therapy. Aim of this study was to evaluate the role of systematically selected tagSNPs from genomic regions coding for six organic cation transporters implicated in transport of metformin with respect to the short-term efficiency. The study involved 102 drug naïve newly diagnosed T2D patients who were treated with metformin monotherapy for 3 months. We genotyped 104 tagSNPs from six metformin transporter genes coding for OCT1, OCT2, OCT3, MATE1, MATE2, and PMAT. Minor alleles of rs3119309, rs7757336l, and rs2481030 located in the intergenic region between *SLC22A2* (OCT1) and *SLC22A3* (OCT3) were significantly associated ($P=1.849\times10^{-6}$ to 2.663×10^{-5}) with metformin inefficiency defined as no decrease of HbA1c blood level after 3 months of treatment. Carriers of risk alleles were 8.4 times more likely to exhibit non-responder phenotype than participants with wild type alleles. Pharmacokinetic study in 15 healthy participants was conducted to investigate the effects of identified polymorphisms on kinetics of plasma and erythrocytes metformin after acute administration in healthy subjects. Subjects with combined risk alleles of polymorphisms rs3119309, rs7757336, and rs2481030 showed strongly reduced AUC_∞ of metformin exposure. In conclusion we have identified for the first time strong association between metformin non-response and three SNPs located in the $5'$ flanking regions of the *SLC22A2* (OCT2) and *SLC22A3* (OCT3). These results indicate the importance of metformin transporters in the short- term efficiency of metformin.
Disclosure
This work was supported by State Research Programme BIOMEDICINE.

DOI: 10.1530/endoabs.37.EP522

EP523

Abstract withdrawn.

DOI: 10.1530/endoabs.37.EP523

EP524

Hyperosmolar hyperglycaemic state and diabetic ketoacidosis: a 5-year retrospective study in a university hospital

Claudia Coelho, Catarina Nunes, Vera Fernandes, Maria Luísa Pinto, Selma B Souto & Olinda Marques
Hospital de Braga, Braga, Portugal.

Introduction
Hyperosmolar hyperglycaemic state (HHS) and diabetic ketoacidosis (DKA) are the two most serious acute metabolic complication of diabetes mellitus (DM). The authors propose to characterise the admissions for HHS and DKA at a univeristy hospital.
Methods
An observational, descriptive, and retrospective study in adults admitted to the hospital between January 2009 and October 2013 due to HHS and DKA. The information was accessed via the patients' electronic records. Statistical analysis was carried out using SPSS.
Results
71 patients were admitted with HHS, with a dominance of female patients (62%). The median age was 79 years and 38% were considered to have economic difficulties. A quarter of the patients was unaware they were diabetic. The most common clinical manifestation on admission was prostration (65%) and the precipitating factor infections (47%). On admission, 25% were treated with insulin but when they became orientated this percentage went up to 62%. During their admission, 41% of the patients were referred to endocrinology. The median time of stay was 9 days. One year after discharge, 11% of patients had been readmitted for the same reason and 23% had passed away.
In the case of DKA, 44 patients were admitted, 63% being female patients. The median age was 57 years and 51% were considered to have economic difficulties. Half the patients presented with prostration and in 35% of the cases the precipitating factor was lack of compliance with therapy. The median time of stay was 8 days. A quarter of the patients had already had a previous admission and a year after discharge, 30% had been readmitted for the same reason whilst 22% had passed away.
Conclusion
In 5 years, 115 patients were admitted com acute complications of DM. The high incidence of readmissions and mortality in the year following discharge as well as the lack of the compliance with therapy in those admitted with DKA are noteworthy. This shows a need for improved assisted care post-discharge in these patients.

DOI: 10.1530/endoabs.37.EP524

EP525

The value of ankle–brachial index in patients above 40 years old with type 2 diabetes mellitus on the diagnosis of peripheral artery disease and the association between peripheral artery disease and chronic diabetes complications

Nur Kebapci & Tugce Nur Turkozu
Eskisehir Osmangazi University, Eskisehir, Turkey.

Peripheral artery disease (PAD); is a chronic occlusive disease in lower extremities. PAD is an important sign of atherosclerosis, and an important predictor of mortality and morbidity during the cerebrovascular and cardiovascular diseases. Since the cardiovascular diseases are the most important cause of death in type 2 DM patients, diagnosing the mortality and morbidity predictor PAD in the early period is very important. The ankle–brachial index is an easy and cheap method to diagnose PAD. In this study, we aim to identify PAD prevalence by measuring ankle–arm index in type 2 DM patients, by compare with arterial Doppler ultrasonography findings of lower extremity and to identify the association between chronic complications of type 2 DM and PAD. 111 type 2 DM patients above 40 years old were included in our study. The PAD prevalence was found to be 19.8%. Dorsalis pedis artery palpation was found to be an important physical exam finding to diagnose PAD. Instead of ABI calculation in the AHA and TASC2 guidelines, there was a stronger correlation between PAD prevalence and the method of dividing the lower systolic blood pressure of dorsalis pedis or tibialis posterior artery by the higher systolic blood pressure of brachial artery. A significant association was found between PAD diagnosed with lower extremity arterial Doppler and age, DM duration, BMI, coronary artery disease, cerebrovascular disease, GFR, albuminuria, uric acid and homocystein levels, insulin resistance, diabetic rethinopaty and vibration test. The ankle–brachial index was found to be a reliable method to diagnose PAD.

DOI: 10.1530/endoabs.37.EP525

EP526

Bone mineral density in patients with type 1 diabetes mellitus by DEXA and QCT

Eleftheria Mparmpa[1], Spyros Karamagiolis[2], Stelios Tigas[3], Parthena Navrozidou[4], Marianna Vlychou[4], Ioannis Fezoulidis[4], Georgios N Koukoulis[1] & Alexandra Bargiota[1]
[1]Department of Endocrinology and Metabolic Diseases, University of Thessaly, Larissa, Greece; [2]General Hospital of Larissa, Larissa, Greece; [3]Department of Endocrinology, University of Ioannina, Ioannina, Greece; [4]Department of Radiology, University of Thessaly, Larissa, Greece.

Introduction
Type 1 DM (T1DM) has been associated with low bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DEXA) but not with quantitative computed tomography (QCT). QCT provides a three-dimensional image and measures bone's volume directly as density, independent of the surrounding tissues. The purpose of this study was to evaluate BMD in patients with T1DM using DEXA and QCT.
Methods/design
We studied 81 patients with T1DM (group D) (age: 36+9.7 years, M/F: 32/49) and 70 healthy controls (group C) matched for age, sex, and BMI. In both groups, we measured HbA1c, lumbar spine (LS), and femoral neck (FN) BMD by DEXA and LS BMD by QCT.
Results
Mean BMI (kg/m^2) was similar in both groups (D: 23.3+8.1 vs C: 23.7+8.3, $P=0.39$). In group D, mean duration of diabetes was 16.1+9.9 years and mean HbA1c was 8.1+1.3%. BMD (g/cm^2) and z-score measured by DEXA were lower in group D compared to group C at LS (1.02±0.20 vs 1.05±0.14, $P=0.03$) (−0.31±1.61 vs 0.78±1.76, $P=0.01$) and at FN (0.69±0.12 vs 0.89±0.11, $P=0.043$) (−0.1+1.47 vs 1.35±1.04, $P=0.037$). Also, LS z-scores measured by QCT were lower compared to DEXA (D: −0.16+1.08 vs −0.31±1.61, $P=0.022$). The lower DEXA z-scores were negative correlated with young onset age ($r=-0.74$, $P=0.021$) and longer duration of T1DM ($r=-0.78$, $P=0.032$) but not with glycaemic control ($r=0.36$, $P=0.18$). In group D, DEXA detected 9/81 patients (11.1%) with osteopenia and 1/81 with osteoporosis (1.2%) at LS and 5/81 (6.2%) with osteopenia and 1/81 with osteoporosis (1.2%) at FN. In contrast, QCT has detected 14/81 patients (17.3%) with osteopenia and 2/81 patients (2.5%) with osteoporosis at LS.
Conclusion
T1DM is associated with lower BMD compared to controls with both methods used. The choice of measuring method may define a different degree of bone loss.

DOI: 10.1530/endoabs.37.EP526

EP527

Is early measurement of HbA1c useful for the prediction of treatment response in type 2 diabetes?

Michaela Luconi[1], Besmir Nreu[2], Jinous Samavat[1], Agostino Ognibene[2], Matteo Monami[2] & Edoardo Mannucci[2]
[1]University of Florence, Florence, Italy; [2]Careggi University Hospital, Florence, Italy.

HbA1c, which is correlated with 3-month mean glycaemia, is usually measured every 3–6 months. Effects of variations of treatment are routinely assessed through HbA1c not earlier than 3 months. Glycated albumin (GA) has been proposed as an indicator of shorter-term (2-week) glucose control Aim of the present pilot study was to explore the possibility of predicting 3-month HbA1c by measuring HbA1c or GA at 15–30 days. Twenty-seven metformin-treated patients with type 2 diabetes initiating a pharmacological treatment other than insulin were enrolled after written informed consent. The patients (16M:11F, aged 64.7±10.1 years) had a duration of diabetes of 8.6±8.5 years, baseline HbA1c 59.0±12.0 mmol/mol. The prescribed treatment was maintained throughout the 3-month follow-up. HbA1c and GA were measured at baseline, 15, and 30 days, and HbA1c only at 90 (±3) days. HbA1c at 90 days (50.0±7.2 mmol/mol) was significantly ($P<0.001$) reduced from baseline (59.0±12.0 mmol/mol). A significant reduction was already present at 15 days (56±7.8 mmol/mol, $P<0.01$) and confirmed at 30 days (53.0±7.0 mmol/mol, $P<0.001$). A similar pattern was found for GA, which was significantly lower at 15 (28.8±10.8%, $P=0.03$) and 30 (27.0±9.8%, $P<0.001$) days than at baseline (31.9±11.3%). Variations of both HbA1c and GA at 15 days showed a significant correlation with 90-day variation of HbA1c: $R=0.895$, $P=0.001$ and $R=0.418$, $P=0.030$, respectively, confirmed at 30 days. The early identification of patients

not adequately responding to the prescription of a new drug could be very useful for clinicians, allowing a greater timeliness in further modifications of therapy. This pilot study suggests that a measurement of HbA1c as early as 15 days from the start of treatment can accurately predict 3-month results being of help for the assessment of treatment response. This result deserves to be further verified in larger samples.

DOI: 10.1530/endoabs.37.EP527

EP528

Sex steroids levels and body composition in male patients with type 1 diabetes mellitus

Eleftheria Mparmpa[1], Spyros Karamagiolis[2], Stelios Tigas[3], Parthena Navrozidou[4], Marianna Vlychou[4], Ioannis Fezoulidis[4], Georgios N Koukoulis[1] & Alexandra Bargiota[1]
[1]Department of Endocrinology and Metabolic Diseases, University of Thessaly, Larissa, Greece; [2]General Hospital of Larissa, Larissa, Greece; [3]Department of Endocrinology, University of Ioannina, Ioannina, Greece; [4]Department of Radiology, University of Thessaly, Larissa, Greece.

Introduction
Limited data exists regarding testosterone levels in type 1 diabetes mellitus (T1DM). The objective of this study was to evaluate serum sex steroids levels and body composition using dual energy X-ray absorptiometry method (DEXA) in male patients with T1DM.
Methods/design
We studied 36 male patients with T1DM (group D) (age: 35.3 + 11.66, years) and 35 healthy control (group C) matched for age, sex, and BMI. In both groups waist circumference (WC), HbA1c, total testosterone (TT), sex hormone-binding globulin (SHBG), LH, FSH, and IGF1 were measured. Calculated free (cFT) and bioavailable testosterone were estimated by standard formulas. Moreover, body composition was determined by DEXA and was calculated central abdominal fat (CAF).
Results
Mean BMI (kg/m^2) and mean WC (cm) were similar in both groups (D: 25.8 + 3.44 vs C: 25.2 + 3.2, $P = 0.37$) and (D: 94.5 + 9.6 vs C: 92.9 + 8.7, $P = 0.24$). In group D, mean duration of DM was 16.8 + 10.5 years and mean HbA1c was 8.2 + 1.1%. We did not observe significant difference in TT, LH, and FSH levels between two groups. Group D had significantly lower SHBG (nmol/l) and IGF1 (ng/ml) levels than group C (39.57 + 7.5 vs 37.32 + 6.9, $P = 0.043$ and 144.7 + 30.1 vs 180.2 + 27.1, $P = 0.031$). Lower cFT (nmol/l) and bioT (nmol/l) levels were observed in group D compared to C but but did not reach clinical significance (0.608 + 0.136 vs 0.812 + 0.119, $P = 0.052$ and 14.7 + 2.3 vs 15.2 + 2.5, $P = 0.057$). Total fat and CAF were similar in both groups. CAF was negative correlated to TT and FT levels ($r = -0.73$, $P = 0.029$ and $r = -0.79$, $P = 0.034$). In group D, 2/36 (5.6%) had TT levels below the normal range after adjustment for age and BMI but none of group C.
Conclusion
Patients with T1DM seem to have a tendency to hypogonadism and its existence mainly occurred in association to obesity.

DOI: 10.1530/endoabs.37.EP528

EP529

Diabetic 'holiday' foot: cautionary tales of sun, sandals, and risk

James O'Hare[1], Fiona Nolan[1], Eamon Kavanagh[2], Paul Burke[2] & Elizebeth Carraig[2]
[1]Department of Endocrinology, Univesity Hospital Limerick, Limerick, Ireland; [2]Department of Vascular Surgery, Univesity Hospital Limerick, Limerick, Ireland.

Diabetic polyneuropathy is the most prevalent complication of diabetes. Diabetic foot lesions become limb threatening from a combination of injury, infection and impaired micro and macrocirculation. When diabetic patients go on holiday they usually change their routine and may become careless in routine care of their feet. We report a case series of seven middle aged Irish born diabetic male patients who developed serious foot lesion on holiday. They were identified from the podiatry services of a regional centre over 3 years. The median age was 59, range 57–68 years. Six of seven had type 2 diabetes duration 1–30 years. HbA1c ranged from 7 to 10.6%, median: 9.6%. One smoked. All had signs of peripheral polyneuropathy. Two had Charcot joint. Six of seven had a holiday in a warmer climate. The median delay to seeking care was 2 weeks, range 1 day–12 weeks. Lesions had a variety of sites, they were bilateral in 5/7. Lesions included: massive blister, ulceration, pressure necrosis, and maceration. Infection was present in six of seven. Two of seven required partial foot amputation. Two had a hospital stay over 60 days. Healing took 4–20 weeks. All walked more than was their customary habit and often on uneven surfaces. One walked barefoot for a week incurring deep planter ulceration. Another wore tight golf shoes incurring pressure necrosis. One walked extensively in an orthopaedic boots. The majority wore sandals resulting in tissue maceration and infection. All reported heat as an aggravating factor. Middle-aged diabetic males with polyneuropathy seem particularly vulnerable on holiday. The common factors were: i) a change in or inappropriate footware, ii) unaccustomed walking and surfaces, and iii) heat causing tissue maceration. Patient education should emphasis the hazards of holidays in high-risk patients.

DOI: 10.1530/endoabs.37.EP529

EP530

Macrovascular complications in type 1 diabetes mellitus

Ennaifer Houda, Chaker Fatma, Ben Salah Dhouha, Hamdi Med Salah, Yazidi Mariem, Chihaoui Malika & Slimane Hedia
Department of Endocrinology and Diabetes, Rabta University Hospital, Tunis, Tunisia.

Introduction
Cardiovascular complications are well known in type 2 diabetes with other factors of cardiovascular disease. Recently, with the intensive treatment of type 1 diabetes, many studies have focused on macrovascular complications in type 1 diabetes. The aim of our study was to determine the long-term cardiovascular risk factors and macrovascular complications in type 1 diabetic patients.
Patients and methods
A retrospective study involving 45 patients hospitalised in Rabta Endocrinology Department between 1997 and 2005 for type 1 diabetes. We noted after a minimum follow-up of 10 years the appearance of cardiovascular events. We also reported cardiovascular risk factors such as family history of cardiovascular events, smoking, obesity, dyslipidaemia, and hypertension, insulin dose, and glycaemic control.
Results
Our patients were 21 men and 24 women. The average age of our patients at diagnosis was 25.3 years (10–50), their mean BMI was 22 (15.8–26.95). The average waist circumference was 75.88 cm. Ten patients were smokers, four patients had a family history of cardiovascular events. The lipid profile was normal in all patients. The mean insulin dose was 1 UI/kg per day (0.16–1.54). The mean duration of diabetes in our patients was 14 years (range 10–30). Six patients developed hypertension. After a follow-up of 10 years, the mean BMI was 20 (18.19–38) and the mean insulin dose was 1 UI/kg per day. The mean of HbA1c was 10%. We didn't report any macrovascular events in our patients.
Conclusion
Type 2 diabetes is usually associated with other cardiovascular risk factors related to the metabolic syndrome. Poor glycaemic control is a common factor to both types 1 and 2 diabetes. Intensive treatment of type 1 diabetes with a strict glycaemic control result often in a long-term overweight. Comprehensive prevention beyond glycaemic control is necessary to prevent the occurrence of cardiovascular events in type 1 diabetes.

DOI: 10.1530/endoabs.37.EP530

EP531

Is dyslipidaemia adequately controlled in type 2 diabetics in primary care? Analysis of 183 patients

Carmen Maria Cortes-Salazar[1] & Jose Carlos Fernandez-Garcia[2]
[1]Badolatosa Primary Care Centre, Seville, Spain; [2]Endocrinology Department, Virgen de la Victoria University Hospital, Malaga, Spain.

Objectives
To evaluate the degree of control of atherogenic dyslipidaemia in patients with type 2 diabetes mellitus (T2DM).
Methods
Retrospective cohort study which included patients with T2DM followed in a primary care setting. Patients were classified according to the following criteria: strict control of dyslipidaemia (LDL <100 mg/dl and triglycerides <150 mg/dl), partial control of dyslipidaemia (LDL ≥ 100 mg/dl or triglycerides ≥ 150 mg/dl), or absence of control of dyslipidaemia (LDL ≥ 100 mg/dl and triglycerides ≥ 150 mg/dl). Treatment with lipid-lowering drugs (statins, fibrates, nicotinic acid, and ezetimibe) was also collected.
Results
183 patients were included, with a mean age of 62.1 ± 8.3 years (58.4% women). After stratification of patients according to previous criteria, only 32% of patients had strict control of dyslipidaemia, 43% had partial control of dyslipidaemia, and 25% had absence of control of dyslipidaemia. Associated lipid-lowering treatment was present in 72% of patients with strict control, in 81% of patients with partial control and in 90% of patients with absence of control.
Conclusions
Despite the high rate of lipid-lowering therapy in patients with T2DM, a significant percentage of patients do not achieve recommended lipid goals.

DOI: 10.1530/endoabs.37.EP531

EP532

Evaluation of plantar pressure and force in diabetes using Tekscan F-Scan in-shoe foot force and gait analysis system

Ie Byung Park, Soojung Lee, Suneung Kim & Gyucheol Han
Gachon University Gil Medical Center, Incheon, Republic of Korea.

Background
Evaluation of plantar pressure is useful for detecting functional abnormality of foot, especially in diabetic patients. The aim of this study was to evaluate plantar pressure and force in diabetic patients using Tekscan F-Scan in-shoe foot force and gait analysis system.
Methods
Plantar pressure and force were measured by selecting an area of interest under the six areas of the foot: hallux, first metatarsal, second metatarsal, 3–5 metatarsal, midfoot and heel based on previous reports. 65 diabetic patients and age-matched 25 controls were enrolled. Mean age of diabetic patients was 58.4 ± 8.2 years, diabetic duration 8.39 ± 5.26 years, and mean HbA1c 7.7 ± 1.3%, and female 43.1% (28/65). Of the included 65 patients, 16 had diabetic polyneuropathy (DPN), 12 had cardiac autonomic neuropathy (CAN), 31 were without CAN, and 18 had inconclusive tests.
Results
Contact area distribution in diabetics were higher tendency than those in controls. Maximum force distribution was different between two group nearly all areas of foot, especially second metatarsal (109.4 N in DM vs 72.2 N in control, $P<0.001$) and condyle (307.4 N in DM vs 236.9 N in control, $P<0.001$). Pressure average distribution were similar differences between two groups. Right-to-left foot unbalancing of force and pressure in diabetics were showed compared with controls.
Conclusion
Evaluation of plantar pressure is useful for diabetic foot abnormalities. Plantar force and pressure distributions in diabetics are higher than those in controls, especially, in second metatarsal and condyle area. This method may be useful to detect diabetic foot and ulcerative disease early.

DOI: 10.1530/endoabs.37.EP532

EP533

Knowledge assessment of diabetic patients about their disease: a prospective study

Senda Ouerdani, Ines Slim, Amel Maaroufi, Yosra Hasni, Maha Kacem, Koussay Ach, Molka Chaieb & Larbi Chaieb
Department of Endocrinology, Sousse, Tunisia.

Introduction
Therapeutic education of diabetic patients is an integral part of management care of the disease and a permanent way to empower patients and to promote their self-care. The purpose of this study is to evaluate the knowledge of diabetic patients about their disease.
Patients and methods
This prospective study has been conducted during 9 months and included 312 patients with type 2 diabetes mellitus (T2DM) diagnosed at least 3 months ago. All patients were followed in third care consultation without history of structured education program. Clinical and biological data in addition to an Individual Knowledge Scale (SKILLD). A value above 50% reflects a good level of knowledge.
Results
The mean age was 54-year-old and 61% of patients were females. The average of T2DM history was of 11 years with a mean HbA1c of 9.35 ± 1.85%. Symptoms of hypoglycaemia were known by 58% of patients, but its immediate management was only known by 41% of patients. Education on lifestyle rules revealed poor knowledge in 67% of our patients. HbA1c target was unkown in 82% of patients. The average score on SKILLD was at 37 ± 26%. A score >50% was observed in 32.4% of patients. SKILLD value was positively correlated with education level ($r=0.661$; $P<0.001$), and negatively correlated with duration of diabetes and HbA1c ($r=-0.384$; $P<0.001$ and $r=-0.497$; $P<0.001$ respectively). Patients with low SKILLD scores had significantly higher HbA1c (9.78% vs 8.45%, $P<0.001$) and higher age (54.07-year-old vs 40.55-year-old, $P<0.001$) compared to patients with high SKILLD score.
Conclusion
Our study shows knowledge lack about diabetes. This may reflects the difficulty of education during consultation probably because time limitation. We insist through these results on the need of a complementary structured and multidisciplinary therapeutic education.

DOI: 10.1530/endoabs.37.EP533

EP534

Diabetic foot infection: study of 109 patients

Faten Hadj Kacem, Mouna Ammar, Nadia Charfi, Nesrine Cheikrouhou, Fatma Mnif, Mouna Mnif, Nabila Rekik & Mohamed Abid
Department of Endocrinology, Sfax, Tunisia.

Introduction
Diabetic foot infection (DFI) is a major public health problem, both for its morbid clinical consequences mainly ulcers and the economic social cost due to repeated hospitalisations and the high rate of amputation.
Objectives
Analyse the clinical presentation of DFI, study risk factors of developing this infection and describe the therapeutic management.
Materials and methods
Retrospective study spread over 8 years old, of 109 patients hospitalised in the University Hospital of Endocrinology of Sfax and who had a DFI.
Results
The average age of patients was 57.5 years (25–82). Sex ratio was 2.02. Most patients were type 2 diabetics (87.2%) with diabetic history of more than 15 years in 34% of cases. A history of hospitalisation for diabetic feet before the study period was found in 39.4%. On admission diabetes were poorly controlled in the majority of our patients. Among the chronic microangiopathic complications, we found neuropathy (64.2%), nephropathy (20.2%), and retinopathy 37.6%. Macroangiopathic complications were dominated by arteriopathy of the lower limbs in 20.2%. The DFI were unique or multiple. It was 'non-threatening member' infection in 64.2%, dominated by infected wounds in 57.1%. The infection was severe, dominated by infected gangrene in 33%, followed by infected plantar ulcer in 22%. Samples for bacteriological test were performed in 29 patients. The bacteria involved were dominated by *Staphylococcus* 20.7% and gram-negative bacteria in 17.2%. 105 of our patients received an antibiotherapy. The association amoxicillin–clavulanic acid +/− ciprofloxacin were prescribed in first intention in 47%. The average duration of antibiotherapy was 9.7 days in case of infection 'non-threatening member' and 17.3 days for severe infection. Surgical treatment was performed in 45%. Conservative treatment or amputations were done in 15 and 30% cases respectively.
Conclusion
Prevention is the only way to reduce morbidity caused by lesions of the diabetic foot.

DOI: 10.1530/endoabs.37.EP534

EP535

Diabetes and ischaemic stroke: prospective study in hospitalised patients

Ana Margarida Monteiro[1], Cátia Cabral[2], Vera Fernandes[1], Marta Alves[1] & Olinda Marques[1]
[1]Department of Endocrinology, Hospital de Braga, Braga, Portugal; [2]Department of Internal Medicine, Hospital de Braga, Braga, Portugal.

Introduction
Diabetes mellitus (DM) is a major risk factor for stroke and has been shown that diabetic patients who suffer stroke have a worse prognosis, with greater morbidity and mortality.
Objectives
Determination of the prevalence of DM in hospitalised patients for ischaemic stroke. Comparison of demographic variables, complications prevalence, length of hospital stay and in-hospital mortality among diabetic and non-diabetic patients. Assessment of glycaemic control and therapy used in the treatment of DM.
Methods
Observational, analytical, and prospective study of hospitalised patients for ischaemic stroke in Hospital de Braga between August and November 2013. Statistical analysis: SPSS v.20.
Results
Of the 134 patients, 30.6% had a previous diagnosis of DM, 79.9% were over 65 years, and 53.7% were women. The median age was 79 years with no statistical significance between groups ($P=0.624$). The median blood glucose at admission was 115 mg/dl, with statistical significance between groups (156 mg/dl vs 108 mg/dl; $P<0.05$). The median hospital stay was 10 days for both groups. Although, not statistically significant, the prevalence of neurological and infectious complications was lower in diabetic patients (24.4% vs 36.6%; $P=0.167$) as well as in-hospital mortality (2.4% vs 10.8%; $P=0.106$). There was no statistical significance between blood glucose on admission, prevalence of complications and in-hospital mortality. In the group of diabetic patients, the median HbA1c was 7.2%. There was no statistical significance between glycaemic control (HbA1c) and prevalence of complications or in-hospital mortality. About DM treatment at admission vs discharge: 61.0% vs 56.1% were treated with oral antidiabetics (OA), 17.1% vs 17.1% with insulin and OA, 9.8% vs 24.4% only with insulin, and 12.2% vs 2.4% without drug therapy.
Conclusion
Glycaemic control in the diabetic group is reasonable, in most patients, assuming the age, pre-existing comorbidities and chronic complications. We admit that the absence of a higher prevalence of complications and mortality in diabetic vs non-diabetic group, may be related to the small sample size.

DOI: 10.1530/endoabs.37.EP535

EP536

Renal disease risk in type 2 diabetic patients with metabolic syndrome

Yllka Themeli[1,2], Myftar Barbullushi[2,3] & Aqif Gjokutaj[2,3]
[1]'IKEDA' Hospital, Tirana, Albania; [2]DC 'Med.al', Tirana, Albania; [3]UHC 'Mother Teresa', Tirana, Albania.

Background
Patients with diabetes mellitus (DM), diabetic nephropathy (DN), and metabolic syndrome (MS) have a high risk of cardiac morbidity and mortality. Thus, identifying and treating risk factors associated with cardiovascular disease in DM may offer the best approach for preventing and delaying adverse renal and cardiovascular outcomes.
Aim
To determine the relationships between MS, DN, and renal function in type 2 DM.
Methods
In our clinic-based kohort study were enrolled 216 type 2 diabetic patients, from which 59% males and 41% females, with a mean age 54 ± 10 years. We analysed MS, detected DN, and estimated glomerular filtration rate (eGFR) during a 4 years period.
Results
Prevalence of both microalbuminuria and macroalbuminuria were higher in subjects with MS, increasing proportionally with the number of MS components. EGFR was lower in subjects with MS than in those without it (84 ± 12 ml/min per 1.73 m^2 vs 90 ± 21 ml/min per 1.73 m^2; $P<0.001$). The lowest eGFR values were found in those with four or more components of MS. Prevalence of low eGFR increased with the stage of DN and was affected by MS only in normoalbuminuric patients. The most important result was that MS was independently associated with DN, but not with low eGFR, after adjustment for all of the individual components of the MS.
Conclusions
In this study we have noted an independent association between MS and DN. This is a strong argument for treating the MS by an intensive therapy, in order to prevent the progression of DN to the renal failure.

DOI: 10.1530/endoabs.37.EP536

EP537

Optimal regimens of the basal-bolus insulin therapy in adolescents with diabetes mellitus of type 1

Galina Galkina, Angelina Voropay, Marina Levkovich, Alexey Afonin, Marina Komkova & Natalia Morozova
Rostov Scientific Research Institute of Obstetrics and Pediatrics, Rostov-on-Don, Russia.

To achieve the optimal glycaemic control in adolescents with type 1 diabetes mellitus (DM1) is a difficult task. The reason is a low compliance of teenagers caused by psychoemotional peculiarities as well as decreased insulin sensitivity due to a physiologically high concentration of contrainsular hormones (androgens, GH, etc.). This study was aimed to determine peculiarities in regimens of the pump insulin therapy that are necessary for achieving treatment goals in adolescents with DM1. 68 adolescents at the age of 14–18 with DM1, who received continuous subcutaneous infusion of insulin (CSII) from 6 months to 6 years, were examined. The patients were subdivided into two groups: i) adolescents with the optimal and suboptimal metabolic control ($n=46$) and ii) adolescents with long-standing poorly controlled DM1 ($n=22$). Compared with patients in group 2, adolescents in group 1 had significantly higher average total daily dose of insulin (group 1 – 70.0 (53.2; 83.8) U and group 2 – 54.0 (46.3; 68.4) U, $P=0.038$), average daily dose of basal insulin (group 1 – 35.2 (24.7; 40.8) U and group 2 – 25.2 (22.7; 32.7) U, $P=0.019$). The average basal-to-bolus ratio from group 1 patients was 51/49%, compared with group 2 patients – 45/55%. Prevalence of bolus insulin in adolescents with poorly controlled DM1 was caused by frequent use of correction boluses in order to lower postprandial hyperglycemia resulting from the excessive intake of carbohydrates. Group 2 patients had a low level of skills which did not allow them to use additional functions of the pump. A large part of group 1 patients adapted pump settings on their own according to their individual peculiarities, physical activity, etc. Thus, well-balanced basal-to-bolus ratio in adolescents on CSII, which can provide improvements in blood glucose management is 51/49%. An important condition is also a high level of compliance and skills of patients, intention to control actively the disease.

DOI: 10.1530/endoabs.37.EP537

EP538

Contribution of haptoglobin and MTHFR polymorphisms to hyperhomocysteinemia and hypercysteinemia in type 2 diabetic patients

Ana Valente[1,2], Manuel Bicho[3,4], Ana Garcia[3], Conceição Gonçalves[3], Rui Duarte[5], João F Raposo[5] & Helena S Costa[1,6]
[1]Unidade de Investigação e Desenvolvimento, Departamento de Alimentação e Nutrição, Instituto Nacional de Saúde Doutor Ricardo Jorge, I.P., Av. Padre Cruz, 1649-016 Lisboa, Portugal; [2]Departamento de Ciências da Nutrição, Universidade Atlântica, Fábrica da Pólvora de Barcarena, 2730 036 Barcarena, Portugal; [3]Laboratório de Genética, Instituto de Saúde Ambiental, Faculdade de Medicina da Universidade de Lisboa, Av. Prof. Egas Moniz, 1649-028 Lisboa, Portugal; [4]Instituto de Investigação Científica Bento da Rocha Cabral, Calçada Bento da Rocha Cabral, 14, 1250-047 Lisboa, Portugal; [5]Associação Protectora dos Diabéticos de Portugal, Rua do Salitre 118-120, 1250-203 Lisboa, Portugal; [6]REQUIMTE/Faculdade de Farmácia da Universidade do Porto, Porto, Portugal.

Introduction
There is a lack of epidemiological data on the distribution of haptoglobin and C677T of MTHFR polymorphisms in Caucasians type 2 diabetic patients. The contribution of these two genetic factors to hyperhomocysteinemia and hypercysteinemia can be useful to prevent cardiovascular events and to reduce public health costs. The aim of this study is to evaluate the contribution of haptoglobin and C677T polymorphisms for hyperhomocysteinemia and hypercysteinemia in Portuguese type 2 diabetic patients with and without angiopathy.
Methods
A population-based case–control study in 150 Portuguese type 2 diabetic patients was performed. The study population: group I – 75 patients with angiopathy and

group II – 75 patients without angiopathy. Homocysteine and cysteine plasma levels were obtained by validated HPLC methods. The haptoglobin polymorphism was identified by PAGE and peroxidase staining and C677T MTHFR polymorphism by PCR and RFLP. Statistical analysis was performed by odd ratio calculation and linear regression model.
Results
The Hp 2-1 was the most prevalent. The CT and TT genotypes were more frequent in group I (46.4%; 7.2%) than in group II (41.5%; 6.2%). The diabetic patients of group I with the genotypes Hp 2-1 or Hp 2-2 had a higher probability to have hyperhomocysteinemia (OR: 4.19; $P=0.021$) and hypercysteinemia (OR: 4.55; $P=0.028$) than diabetic patients from group II. The presence of 677TT and C677T genotypes in group I increased in five times (OR: 5.37; $P=0.040$) the probability to have hyperhomocysteinemia compared to group II. The association between haptoglobin and C677T polymorphisms increased the probability (OR: 4.14; $P=0.004$) of having hypercysteinemia in group I.
Conclusion
The haptoglobin and C677T of MTHFR polymorphisms are associated with a predisposition to hyperhomocysteinemia and can be considered genetic risk factors in angiopathy development of Caucasians type 2 diabetic patients.
Disclosure
A Valente acknowledges the financial support and this study were financially supported by the research project PIC/IC/82957/2007 from Fundação para a Ciência e Tecnologia and by Instituto Nacional de Saúde Doutor Ricardo Jorge, I.P.

DOI: 10.1530/endoabs.37.EP538

EP539

Type IV renal tubular acidosis in type 2 diabetes: case report of 4 patients

Carlos Tavares Bello, Ricardo Castro Fonseca, João Sequeira Duarte & Carlos Vasconcelos
Hospital de Egas Moniz, Lisboa, Portugal.

Introduction
Type IV Renal Tubular Acidosis (Type 4 RTA) is an underdiagnosed condition known to be more frequent in Diabetes Mellitus patients with moderate renal impairment. It is thought to be very common, with an incidence of 3.8% of hospital admissions in some series, being an increasing problem among the elderly and aggravated by polypharmacy.
Methods/design
The authors describe 4 cases of Type 4 RTA associated with type 2 Diabetes diagnosed and followed in the Endocrinology department of Hospital de Egas Moniz.
Results
The population studied had an average age of 67 years, mean Diabetes duration of 8 years and all had arterial hypertension and hypercholesterolemia. All patients were on insulin therapy and had some degree of chronic renal disease. None suffered from coronary artery disease and only one had cerebrovascular disease. 75% had the full microvascular burden (nephropathy, retinopathy and neuropathy). Mean time from hyperkalemia onset and type 4 RTA diagnosis was 17.2 months. Mean glycated hemoglobin during follow up was 8.7%. Mean glomerular filtration (CKD-EPI) rate at type 4 RTA diagnosis was 40.3 ml/min/1.73m^2. The average number of hospital admissions was 5. Only one patient required therapy with fludrocortisone.
Conclusion
Type 4 RTA is often a late diagnosis in type 2 Diabetes. In our small series we documented a high microvascular complication burden. The associated hyperkalemia poses a significant threat to the affected patients, which often have a limited cardiovascular reserve. Timely diagnosis and adequate treatment are essential for optimizing patient care.

DOI: 10.1530/endoabs.37.EP539

EP540

Glycaemic variability and subclinical inflammation in type 2 diabetes: experience of a Portuguese centre in the last decade

Carlos Tavares Bello, Ricardo Castro Fonseca, Ricardo Capitão, Francisco Sousa Santos, João Sequeira Duarte, Manuela Oliveira, Catarina Saraiva, Clotilde Limbert, Carlos Vasconcelos & Jorge Azinheira
Hospital de Egas Moniz, Hospital de Egas Moniz, Portugal.

Introduction
Adequate glycaemic, along with other cardiovascular risk factor control in type 2 Diabetes (T2D), and its beneficial impact on subclinical inflammation is associated with better microvascular outcomes.
Objectives
To analyse the correlation between glycaemic control adequacy and systemic inflammatory markers, renal disease progression and cardiovascular risk factors.
Material and methods
Retrospective cohort observational study of T2D patients ($n=1900$) with a minimum of 2 year follow up in the Endocrinology Department of Hospital de Egas Moniz from the year 2005 until 2014. Patients younger than 18 years of age and/or suffering from secondary diabetes were excluded. Fasting blood glucose and glycated hemoglobin variation were analysed and correlated with blood pressure control and renal function, systemic inflammatory and blood lipid profile markers. Descriptive statistical methods were employed: t-test student, ANOVA for continuous and chi-square for categorical variables.
Results
The patient sample had an average age of 61.2 years, being 59.7% female. A statistical significant relationship was documented between the glycaemic variation and renal disease progression (CKD-EPI P 0.045; spot urinary albumin $P<0.001$), lipid profile (non-HDL Cholesterol $P<0.001$) and inflammatory markers (CPR P 0.028; ESR P 0.01; Leucocyte count P 0.004).
Conclusions
Despite having the known limitations of a retrospective study, the sample size allowed the authors to document a possible association between glycaemic variation, renal disease progression, subclinical inflammation and blood lipid profile.

DOI: 10.1530/endoabs.37.EP540

EP541

Weight and weight variability correlates with subclinical inflammation and comorbidities in diabetes type 2: a retrospective study over the last decade

Catarina Roque, Sequeira Duarte, Rute Ferreira, Filipa Serra, Catarina Moniz, Jorge Azinheira & Carlos Vasconcelos
CHLO, Lisboa, Portugal.

Background
Management of obesity and overweight greatly improves glycemic control in type 2 diabetic (T2DM) patients and also provides positive impact in other cardiovascular risk factors in this population.
Objectives
Evaluate the impact of weight and weight variability in subclinical inflammation and comorbidities of T2DM patients, over the last decade.
Methods
Retrospective study of 1900 patients with T2DM, with a minimum of 2 years of follow-up and five evaluations at our Endocrinology outpatient clinic between 2005 and 2014. Patients under 18 years old, with secondary diabetes and BMI >40 kg/m^2 were excluded. The weight variation was calculated using the S.D. of BMI for each patient with 11.0 ± 0.2 determinations per patient over a mean follow-up of 7.25 ± 1.1 years. The main outcomes of management selected included: BMI, blood pressure, lipid profile, renal function and systemic inflammatory markers. Descriptive statistical methods were applied, *t*-test and Pearson's correlations where used to continuous variables and the χ^2 in categorical ones.
Results
The 1900 patients were aged 61.2 ± 0.3 years at the first observation and 769 were men. There was a statistically significant relationship between BMI and BMI variability for systolic blood pressure ($P<0.001$ and $P=0.036$), BMI for diastolic blood pressure ($P<0.001$), creatinine ($P=0.049$), uric acid ($P<0.001$); albuminuria ($P<0.01$), triglycerides $P<0.001$, HDL ($P<0.001$), and non HDH cholesterol ($P<0.015$); monocytes ($P=0.008$).
Conclusions
This retrospective study has the inherent limitations. Allows an insight to the problem by the data volume. The BMI and its variability in this population was associated with elevation of chronic inflammatory markers (monocytes), creatinine and lipid panel. These data reinforce the importance of weight control in T2DM patients.

DOI: 10.1530/endoabs.37.EP541

Obesity and cardiovascular endocrinology

EP542

Subclinical hypothyroidism and features of metabolic syndrome in Saudi elderly women

Eman Alissa[1] & Gordon Ferns[2]
[1]Faculty of Medicine, Kingabdulaziz University, Jeddah, Saudi Arabia; [2]Medical Education and Metabolic Medicine, Brighton and Sussex Medical School, University of Brighton, Brighton, UK.

To investigate the frequency of subclinical hypothyroidism (SCH) in adults with metabolic syndrome (MetS). To assess whether MetS features were associated with SCH. Study subjects were recruited from consecutive patients attending outpatient clinics within the department of internal medicine at KAUH, Jeddah city, KSA. A case–control study was conducted among 122 elderly women. Each patient was matched with a control whose age did not differ by more than 2 years. Demographic and medical data were obtained. MetS was defined according to the American Heart Association. Continuous data are presented as means ± S.E.M. Differences between subjects with and without MetS were determined by Mann–Whitney's U test and χ^2 tests where appropriate. Univariate relationships were estimates by Spearman's correlation analysis. The level of significance was set at two-sided P values <0.05. The data were analysed using SPSS version 20. The prevalence of SCH was 26% in the MetS group and 15% in the control group ($P>0.05$). The prevalence of SCH increased with age ($r=0.241$, $P<0.01$). All obesity measures were consistently inversely associated with serum TSH level. Subjects with MetS had significantly higher levels of blood pressure, fasting blood glucose, fasting blood profile (except for HDL-C which was significantly lower), and serum insulin than their control counterparts ($P<0.01$). All anthropometric measurements and insulin resistance measures were lower in the control group than in MetS patients ($P<0.01$). C-reactive protein was higher in the MetS patients than their matching controls ($P<0.01$). SCH is increased in patients with MetS, therefore hypothyroidism should be considered in newly diagnosed MetS patients. Of all MetS components, waist circumference was the only component negatively associated with serum TSH levels. Low-grade inflammation was more prevalent among the National Cholesterol Education Program-defined MetS patients than their age-matched controls.

DOI: 10.1530/endoabs.37.EP542

EP543

Controlling the obesity epidemic: where does the pharmacist weigh in?

Edmond Pistja & Alba Themeli
Medical Health Training Center Santa Maria, Lezhe, Albania.

Background
Obesity is a growing health concern in Albania. Obesity has been identified as a key risk factor for many chronic diseases including hypertension, dyslipidaemia and type 2 diabetes mellitus. This study was conducted to investigate the role of community pharmacists in obesity counselling, and to identify the barriers to counselling in Albania.
Methods
It was used a descriptive cross-sectional study involved ten community pharmacies that were selected via stratified and systematic random sampling. A pretested self-administered questionnaire collected information on frequency and comfort level with obesity counselling, and the perceived effectiveness of four aspects of obesity management (diet and exercise, prescribed antiobesity medications, diet foods, and nonprescription products and dietary supplements). Information on perceived confidence in achieving positive outcomes as a result of counselling and barriers to counselling was also collected. Descriptive and Spearman' r analysis were conducted using SPSS version 17. Responses with Likert scale rating 1(low score) to 5 (high score) and binary choices (yes/no) were presented as mean (S.D.) and (95% CI), respectively.
Results
The response rate was 83.6%. The overall mean (S.D.) responses indicated that pharmacists counselled obese patients sometimes to most of the time, 3.67 (1.19) and were neutral to comfortable with counselling about aspects of obesity management, 3.77 (1.19). Respondents perceived obesity management aspects to be somewhat effective, 3.80 (1.05). Of the four aspects of obesity management, diet and exercise, and diet foods were the highest ranked in terms of frequency of counselling, comfort level and perceived effectiveness. Pharmacists were neutral to confident in achieving positive outcomes as a result of obesity counselling, 3.44 (1.09). Overall mean responses of counselling obese patients by pharmacists were positively correlated with their perceived comfort with counseling and perceived effectiveness of obesity management aspects. The most anticipated barriers to obesity counselling were lack of patient awareness about pharmacists' expertise in counselling and pharmacists' opinions that obese patients lack willpower and are non-adherent to weight reduction interventions.
Conclusions
Strengths, weaknesses and barriers related to obesity counselling by pharmacists in Albania were identified, and suggestions were provided to strengthen that role.

DOI: 10.1530/endoabs.37.EP543

EP544

Effect of site of waist measurement on the prevalence of metabolic syndrome

Syed Mohd Razi[1], Manish Gutch[1], Sukriti Kumar[2], Abhinav Gupta[1] & Keshav Kumar Gupta[1]
[1]Llrm Medical College, Meerut, Uttar Pradesh, India; [2]Sgpgi, Lucknow, Uttar Pradesh, India.

Background
The metabolic syndrome is one of the fastest growing epidemics of the modern era in both the industrialised as well as developing world. Waist circumference (WC) is an important component to diagnose metabolic syndrome. Cut off point of WC to diagnose metabolic syndrome is different in.different ethnic groups.
Objective
To study and correlate the variation in prevalence of metabolic syndrome depending on the site of waist measurement and to study the effect of gender on the prevalence of metabolic syndrome with variation of site of waist measurement.
Methods
In a prospective, observational and non interventional study, 1000 patients (550 males and 450 females) were screened, out of which 151 patients found to have metabolic syndrome based on Asian Indian guidelines. Patients with gross ascites, pregnancy, substance abuse and age <20 and >70 years were excluded from study. Waist circumference (WC) of each study subject was taken at four different sites.
Results
The prevalence of metabolic syndrome in study population found to be 15.1%. There is no statistically significant difference between male and female in the age, TG level, systolic and diastolic blood pressure while the difference in HDL levels, and fasting blood sugar levels found to be statistic significance ($P<0.001$).The mean WC was maximum when measured at WC4 in both male and female groups. In males, the sensitivity of detection of metabolic syndrome and PPV were maximum at WC4 and minimum at WC2 while specificity and NPV were same at all four sites.
Conclusion
The females in study population have higher HDL than males while males have higher fasting blood sugar than females. WC4 is statistically the best site for detection of metabolic syndrome in whole population sample and in females but in males the sensitivity is maximally at WC4 but it is not statistically significant.

DOI: 10.1530/endoabs.37.EP544

EP545

Calculating serum LDL cholesterol (LDL-C): comparison of LDL-C measured by direct assay with various formulae by combination of ages, genders, and triglycerides

Joana Menezes Nunes[1,2], Elisabete Rodrigues[1,2], Davide Carvalho[1,2] & João Tiago Guimarães[2,3]
[1]Endocrinology, Diabetes and Metabolism Department, Centro Hospitalar São João, Porto, Portugal; [2]Faculty of Medicine, Porto University, Porto, Portugal; [3]Pathology Department, Centro Hospitalar São João, Porto, Portugal.

Introduction
LDL cholesterol (LDL-C) is a major risk factor for atherosclerosis. The Friedewald formula (FF) is limited by hypertriglyceridaemia. We aimed to correlate serum LDL-C measured by direct assay with serum LDL-C estimated by several formulas: Friedewald (FF): LDL-C = CT-HDL − TG/5; Tsai (TsaiF): LDL-C = TC-HDL − TG/8 (TG/8 represents very-LDL-C); DeLong (DeLongF):

LDL-C = TC-HDL − TG × 0.16 and Chen (ChenF): LDL-C = non-HDL-cholesterol × 0.9 − TG × 0.1; and analyse LDL-C estimated values by combination of age, gender and triglycerides (TG).
Methods
Statistical analysis of 52 925 lipid profiles performed in our laboratory (SPSS.v21; Mac). Data are expressed in means ± s.d.s. Student's *t*-test, Pearson's correlation and linear regression were used for a statistical significance <0.01.
Results
For TG $\leq$4.5 mmol/l ($n=51\,975$), LDL-C measured by direct assay was 3.12 ± 0.96 mmol/l (120.8 ± 37.0 mg/dl), by FF 3.07 ± 1.11 mmol/l (118.6 ± 42.8 mg/dl), ChenF 3.26 ± 1.14 mmol/l (126.2 ± 44.2 mg/dl), TsaiF 3.32 ± 1.13 mmol/l (128.3 ± 43.6 mg/dl) and DeLongF 3.20 ± 1.11 mmol/l (123.8 ± 43.1 mg/dl). Linear regression showed a significant ($P<0.001$) better correlation ($\rho=0.947$, $r^2=0.897$) between the measured and calculated LDL-C by the ChenF. Regarding age, ChenF revealed more accurate results. For TG >4.5 mmol/l ($n=950$), LDL-C measured by direct assay was 3.88 ± 1.32 mmol/l (150.1 ± 51.1 mg/dl), by FF 2.39 ± 2.50 mmol/l (92.4 ± 96.8 mg/dl), ChenF 4.13 ± 1.93 mmol/l (159.8 ± 74.8 mg/dl), TsaiF 3.62 ± 2.01 mmol/l (140.2 ± 77.8 mg/dl) and DeLongF 3.05 ± 2.20 mmol/l (117.9 ± 85.1 mg/dl). TsaiF showed the best significant correlation ($\rho=0.849$, $r^2=0.720$). ChenF revealed significant better correlations for children and elderly and TsaiF for adults from 18 to 64 years. Regarding gender, linear regression showed a significant better correlation for ChenF for both TG categories.
Conclusions
FF underestimates LDL-C and the other formulas overestimate it. For patients with TG $\leq$4.5 mmol/l, ChenF provided more accurate for all studied groups. For TG > 4.5 mmol/l, TsaiF showed better correlation but regarding age ChenF revealed to be better for children and elderly and TsaiF for middle age patients. Our results suggest that TsaiF and ChenF may be more suitable for LDL-C estimation, even in the presence of moderate to severe hypertriglyceridaemia.

DOI: 10.1530/endoabs.37.EP545

EP546

Glucose metabolism regulation in morbidly obese patients and in patients after biliopancreatic diversion

Natalya Mazurina[1], Ekaterina Troshina[1], Natalya Ogneva[1] & Yuri Yashkov[2]
[1]Endocrinology Research Center, Moscow, Russia; [2]Endosurgery and Lithotripsy Center, Moscow, Russia.

Introduction
Morbid obesity (MO) is associated with high frequency of type 2 diabetes mellitus (T2DM). Biliopancreatic diversion (BPD) is bariatric operation that results in rapid T2DM remission and increased GLP-1 levels. The aim of the study was to compare non-diabetic MO patients with normal weight controls and with patients who underwent BPD more than 2 years ago.
Methods
Blood glucose levels, IRI, GLP-1, GIP and glucagon were measured during the oral glucose tolerance test (OGTT) in three groups of patients. Patients of the 1st group (MO) had BMI >40 ($n=22$) and no history of diabetes mellitus. Patients after BPD were included in the 2nd group ($n=23$), post-operative period median was 4.7 years (2.3–7.2). The 3rd group were normal weight controls ($n=22$).
Results
Impaired glucose metabolism was revealed in 68.2% of MO patients ($n=10$). In MO group fasting glucose, IRI and HOMA-IR were maximal ($P<0.001$). MO patients had higher fasting and stimulated GIP and glucagons levels. In the BPD patients postprandial glucose (120 min) was lower, in 17.4% we found postprandial hypoglycemia (<2.8 mmol/l). Stimulated IRI concentration was significantly higher in the BPD group ($P=0.026$). Fasting and stimulated GLP-1 were significantly higher in BPD ($P=0.037$ and $P=0.022$, respectively).
Conclusion
Hyperglucagonaemia, increased GIP levels and decreased GLP-1 levels are observed in MO. Glucose intolerance and insulin resistance incidence is higher in MO patients. Stimulated plasma IRI and GLP concentrations are significantly increased in BPD patients.
Disclosure
This work was supported by the Russian Foundation for Basic Research (grant № 11-04-00946).

DOI: 10.1530/endoabs.37.EP546

EP547

The relationship between the subclinical target organ damage and the levels of ischemia-modified albumin in hypertensive patients

Nihal Ozkayar[1], İhsan Ates[1], Fatma Akyel[1], Cüneyt Tayman[2], Mehmet Namuslu[3], A Nurdan Barça[4], Serdar Akyel[5] & Fatih Dede[1]
[1]Ankara Numune Education and Research Hospital, Ankara, Turkey; [2]Department of Neonatology, Denizli Denizli Goverment Hospital, Denizli, Turkey; [3]Department of Medical Biochemistry, Turgut Ozal University Medical School, Ankara, Turkey; [4]Department of Radiology, Ankara Numune Education and Research Hospital, Ankara, Turkey; [5]Department of Cardiology, Ankara Numune Education and Research Hospital, Ankara, Turkey.

Aim
To investigate the relationship between the presence of subclinical target organ damage (STOD) and the levels of ischemia-modified albumin (IMA) in hypertensive patients.
Methods
The study included a total of 106 patients, 53 with STOD and 53 without STOD. STOD was deemed present if fundus examination revealed a grade 3–4 retinopathy; the left ventricular mass index (LVMI) was >95 g/m^2 in females and >115 g/m^2 in males at echocardiography; carotid intimal media thickness (CIMT) was $\geq$0.9 mm; and 24-h urine had 30–300 mg albumin. IMA levels were assessed by spectrophotometric method using albumin cobalt binding test. All patients underwent ambulatory blood pressure monitoring (ABPM) for 24-h.
Results
The mean whole-day systolic blood pressure was higher in patients with STOD (128.19 ± 15.9 vs 118.55 ± 10.5, respectively $P=0.001$). The mean diastolic blood pressure was similar in both of the groups ($P>0.05$). The mean IMA level was higher in patients with STOD (0.63 ± 0.09 vs 0.53 ± 0.1 respectively $P=0.013$).
Conclusion
Elevated IMA in patients with STOD is consistent with the role of ischemia and oxidative stress in development of target organ damage in hypertensive patients, and suggests that IMA can be used as an indicator to predict the presence of STOD.

DOI: 10.1530/endoabs.37.EP547

EP548

The relationship between socioeconomic level, and the prevalence of masked hypertension and asymptomatic organ damage

İhsan Ates[1], Mustafa Altay[1], Mustafa Kaplan[1], Nihal Ozkayar[2], Güvenç Toprak[1], M Erdem Alagüney[1] & Adem Ozkara[3,4]
[1]Internal Medicine Department, Ankara Numune Education and Research Hospital, Ankara, Turkey; [2]Nephrology Department, Ankara Numune Education and Research Hospital, Ankara, Turkey; [3]Family Medicine Department, Hitit University Medical Faculty, Çorum, Turkey; [4]Family Medicine Department, Ankara Numune Education and Research Hospital, Ankara, Turkey.

Background
This study aimed to determine the prevalence of masked hypertension (MHT) and its association with asymptomatic organ damage (AOD) in a low socioeconomic district of Ankara, Turkey.
Material and methods
Data obtained from the medical records of 712 patients with no known diagnosis of hypertension that presented to a polyclinic due to symptoms related to elevated blood pressure (BP) and were screened for MHT were retrospectively reviewed. The essential hypertension (EHT) included 86 patients screened for AOD. The presence of AOD in patients diagnosed with MHT and the EHT group was recorded.
Results
Among the 712 patients, 206 were diagnosed with EHT and among the remaining 506 patients, 73 were diagnosed with MHT. The patients with MHT had a significantly higher left ventricular mass index, carotid intima media thickness, and 24-h urinary microalbuminuria level (all indicators of AOD) than those with EHT.
Conclusion
A significantly higher percentage of patients with MHT had AOD, as compared with those with EHT, in a low socioeconomic district of Ankara. Based on this

finding, we think patients that present with hypertensive symptoms but have a normal BP should be advised to measure their BP at home.

DOI: 10.1530/endoabs.37.EP548

EP549

Management of hypoglycaemia after gastric bypass: a difficult challenge

Julia Silva-Fernández[1], Álvaro García-Manzanares Vázquez de Agredos[1], Francisco Javier Gómez-Alfonso[1], María López-Iglesias[1], Inés Gómez-García[1] & Carolina González-Pereira[2]
[1]Endocrinology Unit, Mancha Centro General Hospital, Alcázar de San Juan, Ciudad Real, Spain; [2]Intensive Unit Care, Central Asturias University Hospital, Oviedo, Asturias, Spain.

Introduction
Postprandial hypoglucaemia with hyperinsulinism after laparoscopic gastric bypass is an uncommon complication with an estimated prevalence of 0.2%. Its treatment includes acarbose, diazoxide, somatostatin and GLP-1 analogues or calcium channel blockers in case a strict diet does not work.
Case report
A 42-year-old woman with history of gastric bypass in 2005 due to severe obesity (preoperative weight 150 kg) attended our clinic 3 years after surgery reporting hypoglycaemic episodes occasionally accompanied by unconsciousness, occurring 3 h after food intake. The episodes resolved after sugar intake. ACTH stimulation test ruled out adrenal insufficiency. A 72-h fasting test was done with no pathological findings. A glucose tolerance test was also performed showing hypoglycaemia and hyperinsulinism. A CT scan of the abdomen did not find pancreatic nodules. Fractionated diet was started, followed by treatment with acarbose. Both measures were ineffective. Lanreotide treatment was subsequently administered with intolerance and no improvement. Diazoxide was titrated achieving only a partial response and the patient was referred to surgery for corporocaudal pancreatectomy in 2013. Pathological examination found diffuse nesidioblastosis. After the surgery, no hypoglycaemic episodes were observed. Moreover, the patient developed diabetes requiring treatment with insulin. One year after pancreatectomy the patient had a relapse of hypoglycaemia episodes even after insulin withdrawal. An overload test with mixed meal showed hyperinsulinaemic hypoglycaemia. Liraglutide 0.6 mg/24 h was prescribed but we had to stop it because of side effects. The patient was referred to a second surgery for total pancreatectomy.
Conclusions
There is no treatment of choice for patients with nesidioblastosis. Medical treatment, including somatostatin and GLP-1 analogues, should be tried before surgery. When medical treatment fails, subtotal pancreatectomy is a good option to control hypoglucaemia and preserve pancreatic function. When hypoglycaemia persists, total pancreatectomy should be considered.

DOI: 10.1530/endoabs.37.EP549

EP550

The impact of the socio-demographic and lifestyle factors on central obesity and overweight status using structural equation modelling: Tehran Lipid and Glucose Study

Sara Jalali-Farahani[1,2], Parisa Amiri[1,2], Mehrdad Karimi[1,3], Safoora Gharibzadeh[3,4], Parvin Mirmiran[5] & Fereidoun Azizi[4]
[1]Research Institute for Endocrine Sciences, Research Center for Social Determinants of Endocrine Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [2]Research Institute for Endocrine Sciences, Obesity Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [3]Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran; [4]Research Institute for Endocrine Sciences, Endocrine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [5]Department of Clinical Nutrition and Dietetics, Faculty of Nutrition Sciences and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Introduction
This study aimed to investigate possible direct and indirect association of socio-demographic and lifestyle factors with central obesity and overweight status in the Tehran Lipid and Glucose Study (TLGS) population.
Methods
After excluding under- and over-reporters, a sample of 2747 TLGS participants (58.3% female) aged $\geq$20 years were recruited in the study. Overweight and central obesity were defined as having BMI $\geq$25 kg/m^2 and waist circumference $\geq$91 cm (Iranian cut-off point) respectively. Socio-demographic factors, lifestyle factors including leisure time physical activity, dietary patterns and daily energy intake were included in the hypothesised model for the testing direct and indirect effects on overweight and central obesity, using structural equation modelling (SEM), conducted by AMOS V20.
Results
Overweight and central obesity were present in 61.6 and 48.1% of respondents, respectively. Fit indices had acceptable fit for the hypothesized model (χ^2/df = 3.13, GFI = 0.98, CFI = 0.97, RMSEA = 0.028). Among lifestyle factors, daily energy intake had a direct effect on overweight and central obesity in both men (β = 0.44 and 0.47 respectively; $P<0.01$) and women (β = 0.33 and 0.33 respectively; $P<0.01$); while, poor dietary pattern had a direct effect on overweight and central obesity, only in men (β = 0.10 and 0.13; $P<0.01$). Of socio-demographic factors, in women, higher age, being married and lower educational level had direct effects on overweight (β = 0.28, 0.15 and $-$0.09 respectively) and central obesity (β = 0.30, 0.05 and $-$0.12 respectively, $P<0.05$); in men however, only higher age and being married had direct effects on overweight (β = 0.14 and 0.18 respectively) and central obesity (β = 0.23 and 0.14 respectively, $P<$ 0.01). Furthermore, lower age and marital status in both sexes and lower education in women had indirect effects on overweight and abdominal obesity via lifestyle factors.
Conclusion
Interventions aiming at some socio-demographic and lifestyle factors may help health policy makers to reduce the burden of obesity among this adult population.

DOI: 10.1530/endoabs.37.EP550

EP551

The influence of metabolic syndrome to cardiovascular events in a 10-year prospective study

Laura Kazlauskiene, Jurate Butnoriene & Antanas Norkus
Lithuanian University of Health Sciences, Kaunas, Lithuania.

The aim of the study was to evaluate frequency of cardiovascular events (myocardial infarction, stroke) among the individuals with metabolic syndrome (MS).
Materials and methods
The study design was prospective. It was started in 2003 to assess the risk factors, clinical components, diagnostic criteria of MS and to determine correlation between MS and neuropsychiatric disorders. At the second stage in 2013 the individuals were repeatedly invited to evaluate cardiovascular pathology that was confirmed by cardiologist and neurologist. The 45 years old and older citizens of Lithuanian district participated in the study. 1115 individuals (562 men and 553 women) were randomly selected in 2003. 538 respondents: 278 (51.70%) men and 260 (48.30%) women participated in the repeated study in 2013. The age of the individuals was 55 to 92 years.
Results
During the study myocardial infarction (MI) was confirmed to 40 (7.43%) individuals taken part in the study, stroke – to 23 (4.28%) individuals. The odds ratio of MI between individuals with MS and without MS was 1.80 (95% CI 1.67–1.97), $P<0.05$. The odds ratio of stroke for individuals with MS and without MS was 2.05 (95% CI 1.21–2.54), $P<0.05$. According to data of the study, occurrence of MI was higher in the group of individuals with MS than to individuals without MS, respectively 23; 9.75% vs 17; 5.63%, $P>$ 0.05. Occurrence of stroke was higher in the group of individuals with MS, accordingly 14; 5.93% vs 9; 2.98%, $P>0.05$. Comparing the frequency of MI between genders, the pathology was found more frequently in women's group: 14; 10.30% vs 9; 9.00%, $P>0.05$. The frequency of stroke was equal in both groups, accordingly 7; 5.15% vs 7; 7.00%, $P>$ 0.05.
Conclusion
Individuals with identified MS have 1.80 and 2.05 times higher statistically significant probability, respectively, for MI and stroke events, than individuals without MS.

DOI: 10.1530/endoabs.37.EP551

EP552

Influence of normal food intake on the lipid profile of diabetic patients

Susana Garrido[1], Raquel Almeida[1], Teresa Pereira[1], Lia Ferreira[1], Helena Neto[1], Joana Vilaverde[1], Fernando Pichel[1], José Carlos Oliveira[2] & Isabel Palma[1]
[1]S. de Endocrinologia, Diabetes e Metabolismo, Centro Hospitalar do Porto, Porto, Portugal; [2]S. de Química Clínica, Centro Hospitalar do Porto, Porto, Portugal.

Introduction
The need to fast for the determination of lipid profile has been discussed in the past years, for several reasons – i) most of the day time is spent in a postprandial state; ii) the lipid concentrations seem to be only slightly affected by a normal meal; both fasting and postprandial can predict cardiovascular risk.
Aim
Determine the influence of normal food intake on the lipid profile of diabetic patients.
Methods
A total of 248 diabetic patients were included (49.6% male; median age 57 years, range 40–79 years), recruited between April/2013 and August/2014 from the Outpatient Diabetes Education Program of Hospital de Santo António, Centro Hospitalar do Porto. Clinical and analytical evaluation took place in two moments (fasting $=t_0$; 2 h after a standard breakfast $=t_1$), with measurements of total cholesterol (TC), LDL cholesterol (LDL-C), HDL-cholesterol (HDL-C) and triglycerides (TG). Paired LDL-C samples of patients with TG >400 mg/dl and outliers (≥ 3 S.D. from the mean) were excluded from the analysis.
Results
TG concentration increased between the two moments (median difference $t_1-t_0=6$ mg/dl, $P=0.002$) but the TC, HDL-C, LDL-C and non-HDL-C did not change significantly (P: 0.69; 0.75; 0.06 e 0,60 respectively). Performing an analysis according to the two therapeutic goals for LDL-C proposed by the ATP III, we found that the proportion of patients with LDL-C $t_0 \geq 100$ mg/dl and LDL-C $t_1 < 100$ mg/dl was 9.3% (5/54); and LDL-C $t_0 \geq 70$ mg/dl and LDL-C $t_1 < 70$ mg/dl of 3.3% (3/91). Similarly, also a small percentage of patients with LDL-C t_0 <100 mg/dl had values of LDL-C $t_1 \geq 100$ mg/dl (8.6%, 5/58). Considering the objective of 70 mg/dl, this percentage reached 14.3% (3/21).
Conclusion
The data presented question the need to fast for the determination of lipid profile. Further studies are needed to confirm these results and to demonstrate an association of postprandial lipid profile and cardiovascular risk in diabetic population.

DOI: 10.1530/endoabs.37.EP552

EP553

The functional parameters of renin-angiotensin-aldosterone system in obese patients

Nadezhda Platonova, Natalya Mazurina, Teona Shvangiradze, Ekaterina Troshina & Gulnara Katzia
Endocrinology Research Center, Moscow, Russia.

Introduction
Renin-angiotensin-aldosterone system (RAAS) plays a significant role in the development of arterial hypertension (AH) in obese patient. Angiotensinogen expression in adipose tissue decreases during fasting and increases in case of overeating, that leads to changes in blood pressure (BP). The aim of the study was to assess the impact of obesity on the activity of RAAS and its role in the development of hypertension.
Methods
60 women, mean age 28.0 ± 2.1 years, BMI 37.7 ± 1.2 kg/m^2 participated in the study. Subjects were divided into groups depending of the AH presence: the 1st group consisted of 28 women with normal BP (systolic BP 115.6 ± 1.28 mm Hg; diastolic 81.0 ± 3.0 mm Hg). 32 women with AH (systolic BP 166.6 ± 5.4 mm Hg; diastolic BP 96.0 ± 3.2 mm Hg) were included in the 2nd group. 15 healthy normal weight women (19–25 years old, BMI 10.4 ± 2.3 kg/m^2) were included in the control group. NaCl consumption not <5 g/day was recommended to all patients. Plasma aldosterone concentration and renin activity were measured by radioimmunoassay with an automatic analyser («Immunotech», France). Blood samples were taken every 4 h during the day (8, 12, 16, 20, 24, 4 h) to evaluate the circadian rhythm of aldosterone secretion.
Results
In all obese patients plasma Na^+ and K^+ concentrations were normal. Urinary potassium excretion did not differ significantly from the control group ($P>0.05$), sodium excretion was significantly decreased ($P<0.05$). Both groups of obese patients have demonstrated low basal plasma renin activity compared with the control group ($P<0.001$). Plasma renin activity values were not significantly different in the 1st and the 2nd groups (1st – 1.4 ± 0.06, 2nd – 1.15 ± 0.004 ng/ml per h, control group 2.18 ± 0.2 ng/ml per h). Morning aldosterone level was increased in the 1st group. At the same time, morning aldosterone level in the 2nd group was higher in comparison with the 1st group and with the control group (1st – 413.8 ± 20.6 pmol/l; 2nd – 664.1 ± 26.6 pmol/l; control group – 290.0 ± 19.6 pmol/l). Circadian rhythm of aldosterone in the control group was characterized by a maximum concentration in the morning hours (4–8 h) and lower concentration during the day, evening and night hours. A circadian rhythm of aldosterone in patients of the 1st group did not differ from the control group, while the 2nd group demonstrated an inversion of the circadian rhythm of aldosterone with maximum at midnight (24.00 h – 960.4 ± 140.7 pmol/l; 8.00 h – 597.6 ± 96.1 pmol/l, $P<0.05$).
Conclusions
1. Plasma aldosterone concentration in the morning hours was elevated in the obese patients without hypertension.
2. Obese hypertensive patients had inverse aldosterone biorhythm with maximum at midnight.

DOI: 10.1530/endoabs.37.EP553

EP554

Enzymes of the vitamin K cycle and progression of calcification in the vessel wall

Natascha Schweighofer[1], Ariane Aigelsreiter[2], Olivia Trummer[1], Martina Graf-Rechberger[2], Nicole Hacker[1], Florian Iberer[3], Doris Wagner[3], Daniela Kniepeiss[3], Philipp Stiegler[3], Thomas Pieber[1], Helmut Müller[3] & Barbara Obermayer-Pietsch[1]
[1]Department of Internal Medicine, Divison of Endocrinology and Metabolism, Medical University of Graz, Graz, Austria; [2]Institute of Pathology, Medical University of Graz, Graz, Austria; [3]Department of Surgery, Division of Transplantation Surgery, Medical University of Graz, Graz, Austria.

Calcification is a physiological process in bone but occurs also pathologically in the vasculature, favouring cardio- and cerebrovascular diseases (CVD). Vitamin K metabolites, particularly K1 and MK-4, are associated with decreased vascular calcification especially in patients with chronic kidney disease. We investigated the expression of components of the vitamin K cycle (VKC) and the MK-4 synthesis (MKS) in aorta and bone of 26 brain dead organ donors in order to identify differences in the expression pattern during atherosclerosis (AS) stages in aortic vascular tissue and to compare these profiles in both tissue types. Gene expression was performed using TaqMan gene expression assays with a LC480 system. Determination of calcification stage was done histologically: (0 (unaffected vessels), 1 (intima thickening), 2 (intima calcification)). VKC enzymes VKOR, VKORL1, GGCX and the chaperone calu and the enzymes NQO1 and UBIAD1, necessary for MKS are both expressed in aortic and bone tissue. In the aorta, gene expression of VKOR, VKORL1, and calu differed significantly between the three atherosclerotic stages ($P=0.040$; $P=0.023$ and $P=0.038$, respectively), whereas the expression of GGCX showed borderline significance ($P=0.060$). In bone, gene expression of VKC and the MKS proteins did not differ in respective AS stages. Comparison of bone and aorta showed only significant differences in gene expression of calu, GGCX and NQO1 in the last stage of intima calcification. We are able to demonstrate that bone and aorta express the components of vitamin K cycle and of MK-4 synthesis. We also show the existence of a different gene expression pattern in AS progression in bone and aorta. These data might lead to a more comprehensive insight into the role of vitamin K metabolising enzymes in vascular calcification.
Disclosure
This work was supported by the Austrian Anniversary Fund (project numbers 13266, 15635) and by BioPersMed (COMET K-project 825329).

DOI: 10.1530/endoabs.37.EP554

EP555

Weight loss with bariatric surgery improves ischaemia modified albumin levels and oxidative status in morbidly obese patients

Adnan Yay[1], Muzaffer Ilhan[1], Saime Turan[2], Ümit Zeybek[2], Ozcan Karaman[1], Ilhan Yaylim[2] & Ertugrul Tasan[1]
[1]Bezmialem University, Istanbul, Turkey; [2]Istanbul University, Istanbul, Turkey.

Introduction
Oxidative stress is one of the possible mechanisms involved in the pathogenesis of the obesity-related metabolic complication. In this study, we aimed to investigate effect of weight loss with bariatric surgery on IMA, high sensitive C-reactive protein (hs-CRP), serum total antioxidant status (TAS), total oxidant status (TOS) levels.
Materials and methods
In this prospective study, plasma IMA, hs-CRP, TAS and TOS levels were measured before and 6 months after laparoscopic sleeve gastrectomy in 60 morbidly obese patients with a BMI of 46.6 ± 6.7 kg/m^2. 43 age-matched healthy subjects with a BMI of 24.6 ± 3 recruited as controls. Metabolic parameters including serum levels of fasting glucose, HbA1c, homeostatic model assessment of insulin resistance (HOMA-IR), C-peptide, LDL, HDL, triglyceride were also measured before and after surgery.
Results
Excess weight loss (EWL) and percentage of EWL were 34.9 ± 10.5 kg and 27.8% in obese patients. Plasma IMA levels before surgery was significantly increased in patients compared to controls ($P<0.05$). We found significantly increased hs-CRP levels in patients compared to controls ($P<0.001$). Plasma IMA and hs-CRP levels were significantly decreased in patients after 6 month of bariatric surgery ($P<0.05$ and $P<0.001$, respectively). At 6th month of surgery, BMI of patients was still significantly higher than controls ($P<0.01$), hs-CRP levels were significantly increased in patients ($P<0.001$) but there was no significant difference in IMA levels. A statistically significant reduction was found in the TOS values after the surgery ($P<0.001$), but there were no significant changes in the TAS levels. Significantly decreased levels of fasting glucose ($P<0.01$), HbA1c ($P<0.001$), HOMA-IR ($P<0.01$), C-peptide ($P<0.001$), LDL-C ($P<0.001$) and triglyceride ($P<0.001$) and increased levels of HDL-C ($P<0.001$) were observed after bariatric surgery.
Conclusion
Our findings supported that weight loss with bariatric surgery improves IMA, hs-CRP, TOS levels and metabolic profile in patients. Along with still higher BMI in patients after surgery, no significant difference in IMA levels between obese and healthy group suggested that bariatric surgery could have beneficial effects on oxidative stress beyond weight loss.
Disclosure
This work was supported by Bezmialem Research Council (grant number 12.2013/25).

DOI: 10.1530/endoabs.37.EP555

EP556

Metformin treatment of hypothalamic obesity: the lesson of two cases

Codruta Nemes[1], Sabina Secara[1], Ioan Stefan Florian[2,3] & Cristina Ghervan[1,3]
[1]Department of Endocrinology, Cluj Napoca, Romania; [2]Department of Neurosurgery, Cluj Napoca, Romania; [3]University of Medicine and Pharmacy, Iuliu Hatieganu, Cluj Napoca, Romania.

Introduction
Hypothalamic obesity is defined as a syndrome of intractable weight gain as a result of hypothalamic lesions. Craniopharyngioma is responsible for more than half of the cases of hypothalamic obesity, but other pathologies can be implied. The syndrome can occur due to the tumour itself or its treatment (surgery or radiotherapy). Metformin is an antidiabetic drug that has also been used to treat nondiabetic obese patients, as it has been demonstrated to promote weight loss. Metformin alone has not been previously tested in patients with hypothalamic obesity.
Case presentation
We present the case of two patients with hypothalamic obesity, which were efficiently treated with metformin. The first case is a 44-year-old woman who has gained 45 kg following surgery for cranyopharyngioma, despite caloric restriction and treatment with sibutramine and then orlistat. When she reached 150 kg, treatment with Metformin was initiated. During treatment she lost 34 kg in 30 months and her insulin resistance decreased significantly. The second case is a patient who was diagnosed at 6.4 years with a suprasellar mixed germ cell tumour (immature teratoma and germinoma). She underwent surgery, radiotherapy and chemotherapy. Following surgery, she developed severe hypothalamic obesity with insatiable bulimia, gaining dramatically 32 kg in 2.5 years. As complication of this major weight gain she had severe insulin resistance, dyslipidaemia, and steatohepatitis. As nutritional intervention and treatment with sibutramine and orlistat failed, treatment with metformin was initiated. After 1 year she lost 21 kg, her lipid profile and insulinaemia improved considerably and her liver enzymes normalised.
Conclusion
Metformin proved to be an efficient and well tolerated treatment in these two patients with hypothalamic obesity, showing that it can be an option in these dramatic cases.
DOI: 10.1530/endoabs.37.EP556

EP557

Glycolysis in septic patients during early ICU hospitalisation shows differences vis-à-vis shock resolution

Ioannis Ilias[1], Sofia Apolonatou[2], Nikitas Nikitas[2], Maria Theodorakopoulou[2], Frantzeska Frantzeskaki[2], Dimitra Vasiliadi[3] & Ioanna Dimopoulou[2]
[1]Department of Endocrinology, E Venizelou Hospital, Athens, Greece; [2]Second Department of Critical Care Medicine, University of Athens Medical School, Attikon University Hospital, Athens, Greece; [3]Second Department of Internal Medicine, University of Athens Medical School, Attikon University Hospital, Athens, Greece.

Introduction
In glycolysis, glucose is converted into pyruvate. Patients with sepsis are prone to numerous metabolic alterations, including changes in carbohydrate metabolism.
Aim
To assess glucose metabolism in septic patients during the first day of ICU hospitalisation and evaluate this vis-à-vis shock resolution.
Subjects and methods
Ten patients with septic shock during the first day of ICU hospitalization were studied; measurements were done every 2 h in blood for glucose and in tissue (with microdialysis (MD)) for pyruvate. Patients with diabetes were excluded. Six patients recovered from shock within 1–9 days. We analyzed the data on a cross-correlation matrix of 2-h' increments of blood glucose and MD pyruvate for patients with shock resolution and no shock resolution separately.
Results
In patients with shock resolution significant correlations were noted for blood glucose vs MD pyruvate (maximum r: $+0.96$, P: 0.004; with pyruvate lagging by 12 h); no significant correlations between blood glucose and MD pyruvate were measured in the patients with no shock resolution.
Discussion
During the first day of ICU hospitalisation septic shock patients who eventually resolved their shock status showed active glycolysis, whereas patients who remained in shock had early on no appreciable glycolysis.
DOI: 10.1530/endoabs.37.EP557

EP558

Renal hemodynamic status in patients with different classes of obesity

Lyndina Maria & Shishkin Alex
Medical Faculty, Saint-Petersburg State University, Saint-Petersburg, Russia.

Introduction and aims
Obesity is associated with increased single-nephron glomerular filtration rate, which may increase the risk of chronic kidney disease (CKD). Several biopsy studies showed the association between obesity and higher prevalence of CKD features, including segmental glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arterial sclerosis. Another approach is to study intra-renal

hemodynamics by ultrasound, where renal parenchymal damage in obesity may be reflected by intra-renal resistive indices.
Methods
We examined 108 patients with different classes of obesity (90 women and 18 men, mean age: 54.62 ± 0.4 years). All patients were divided into three groups (III classes of obesity, divided by BMI). They underwent clinical and laboratory examination, which included lipidogram, insulin, plasma homocysteine levels, microalbuminuria (MAU) in the morning urine. The result was determined directly, without any recalculation. UIA identified in excess of index higher than 20 mg/l. Study of intrarenal blood flow was performed by color Doppler with pulsed doplerometry on the device Aloka SSD-5500. We studied the main and intrarenal renal artery (segmental and interlobar) in the projection of the three segments of both kidneys. We determined the resistive characteristics of the arterial blood flow (RI and PI), calculated automatically by the standard formulas.
Results
The average level of insulin plasma and homocystein exceeded the normal laboratory data in the III class – 31.57 ± 0.41 mE/l ($P < 0.001$) and 18.43 ± 0.57 mol/l ($P < 0.001$). The level of MAU exceeded in the II class – 20.44 ± 0.46 mg/l ($P < 0.05$) and III class – 53.09 ± 7.87 mg/l ($P < 0.001$). In the study of intrarenal blood flow RI and PI in the segmental and interlobar level of the arteries in this groups of patients were above normal values. In the segmental level: I class – RI = 0.64 ± 0.01 ($P < 0.05$) and PI = 0.99 ± 0.2 ($P < 0.001$); II class – RI = 0.71 ± 0.01 ($P < 0.05$) and PI = 1.24 ± 0.03 ($P < 0.001$); III class – RI = 0.70 ± 0.01 ($P < 0.05$) and PI = 1.33 ± 0.04 ($P < 0.001$). In the interlobar level: I class – RI = 0.63 ± 0.01 ($P < 0.05$) and PI = 0.99 ± 0.2 ($P < 0.001$); II class – RI = 0.70 ± 0.01 ($P < 0.05$) and PI = 1.24 ± 0.03 ($P < 0.001$); III class – RI = 0.68 ± 0.01 ($P < 0.05$) and PI = 1.31 ± 0.04 ($P < 0.001$).
Conclusions
These results suggest that obese patients have a sign of intravascular renal resistance and an increased risk for CKD.

DOI: 10.1530/endoabs.37.EP558

EP559

Influence of anthropometric parameters, leptin, adiponectin, and insulin resistance on blood pressure in obese women

Milena Velojic Golubovic, Dragan Dimic, Milica Pesic, Sasa Radenkovic & Danijela Stojic
Clinic of Endocrinology, Clinical Center Nis, Nis, Serbia.

Relationship of body weight and blood pressure is very complex and still incompletely explained. Obesity, especially visceral, is one of the strongest predictors of arterial hypertension. Hypertension is six times higher in obese than in lean people, with its prevalence increases with an increase in BMI progressively. The mechanisms underlying hypertension in obese are not fully defined. The aim of this research was to determine the influence of various parameters on blood pressure and assume the possible pathogenetic mechanisms.
Materials and methods
The study included 90 obese women who were determined of average values of blood pressure, anthropometric parameters, levels of leptin, adiponectin, insulin levels, and HOMA-R index and established their mutual correlation.
Results
The mean values of blood pressure of patients was 146 ± 15.68 mmHg for systolic and 92 ± 10.83 mmHg for diastolic blood pressure. 33% of the subjects were normotensive. Correlation of anthropometric parameters and blood pressure values established their positive correlation, with a statistically significant impact of a waist circumference ($P < 0.001$) and waist/hip ratio ($P < 0.01$). Insulinaemia and HOMA-R index correlated positively and significantly with the values of systolic and diastolic blood pressure ($P < 0.05$). Leptin levels correlated positively and statistically significant with the systolic ($P < 0.001$) and diastolic blood pressure ($P < 0.05$). Correlations between adiponectin levels with the systolic and diastolic pressure are negative and not statistically significant. There is statistical significance of the negative correlation of adiponectin with fasting insulin levels and HOMA-R index.
Conclusion
Waist circumference, waist/hip ratio, insulin resistance, and leptin levels have statistically significant effect on blood pressure, and thus the occurrence of hypertension in obese women. Adiponectin through impact on insulin sensitivity probably contributes to the development of arterial hypertension.

DOI: 10.1530/endoabs.37.EP559

EP560

Galectin-3 and fibulin-1 in systolic heart failure patients with and without diabetes: relation to glucose metabolism and left ventricular contractile reserve

Pernille Holmager[1], Michael Egstrup[2], Ida Gustafsson[3], Morten Schou[4], Jordi Dahl[5], Lars Melholt Ramussen[6], Jacob Møller[5], Christian Tuxen[7], Jens Faber[1,8] & Caroline Kistorp[1,8]
[1]Department of Medicine, Herlev University Hospital, Herlev, Denmark; [2]Department of Cardiology, Rigshospitalet, Copenhagen, Denmark; [3]Department of Cardiology, Hvidovre University Hospital, Hvidovre, Denmark; [4]Department of Cardiology, Herlev Universty Hospital, Herlev, Denmark; [5]Department of Cardiology, Odense Univeristy Hospital, Odense, Denmark; [6]Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark; [7]Department of Cardiology, Bispebjerg Hospital, Copenhagen, Denmark; [8]Faculty of Health and Science, Copenhagen University, Copenhagen, Denmark.

Aims
Diabetic patients with heart failure (HF) have an adverse prognosis, which could be linked with reduced left ventricular (LV) contractile reserve. Galectin-3 (Gal-3) and fibulin-1 are potential biomarkers of fibrosis. The aims were to evaluate the impact of DM on Gal-3 and fibulin-1 levels and the association to LV contractile reserve in HF patients with and without diabetes (DM).
Methods and results
From an out-patient HF clinic 155 patients with systolic HF were included and underwent a low-dose dobutamine echocardiography and blood sampling for analyses of plasma Gal-3 and fibulin levels. Oral glucose tolerance test (OGTT) was performed in non-diabetic HF patients. Based on history of DM and OGTT patients were divided into normal glucose tolerance (NGT) ($n = 95$), impaired glucose tolerance (IGT) ($n = 25$), and DM ($n = 60$).
Results
Galectin-3 levels were 17.9 ng/ml in diabetics ($P = 0.02$) while fibulin-1 levels were not influenced by DM status. Gal-3 was associated with LV contractile reserve in a univariable regression model; standardized β (S.E.M.) ($\beta = -0.19$, $P = 0.03$), but not in a multivariable model including eGFR, ($\beta = -0.04$, $P = 0.66$). Fibulin-1 was not associated with LV contractile reserve in a univariable model ($\beta = -0.06$, $P = 0.51$). HbA1c was independently associated with Gal-3 ($\beta = 0.16$, $P = 0.02$) and fibulin-1 ($\beta = 0.16$, $P = 0.04$) in a multivariable regression model including eGFR.
Conclusion
Gal-3 and fibulin-1 levels were elevated in diabetic HF patients, associated with HbA1c, but not with LV contractile reserve.

DOI: 10.1530/endoabs.37.EP560

EP561

The effect of the type of the bariatric surgery in the lipid profile: an age, sex, BMI, and excess weight loss matched study

Filipe Cunha[1,2], Joana Oliveira[1,2], John Preto[3], Ana Saavedra[1,2], Maria Costa[1,2], Daniela Magalhães[1], Rita Bettencourt-Silva[1], Paula Freitas[1,2], Ana Varela[1,2] & Davide Carvalho[1,2]
[1]Serviço Endocrinologia, Diabetes e Metabolismo do Centro Hospitalar São João, Porto, Portugal; [2]Faculdade de Medicina da Universidade do Porto, Porto, Portugal; [3]Serviço de Cirurgia Geral do Centro Hospitalar São João, Porto, Portugal.

Introduction
Bariatric surgery improves lipid profile. A still unanswered question is whether this improvement is merely weight dependent or also results from factors inherent to specificities of the bariatric procedure itself. We aimed to study lipid profile 1 year after bariatric surgery and compare its changes between the different procedures in patients matched for initial weight and for weight loss.
Methods
We retrospectively analysed patients submitted Roux-en-Y gastric bypass (RYGB), adjustable gastric banding (AGB), or sleeve gastrectomy (SG) between 2010 and 2013. Patients were matched for age (±5years), sex, pre-surgery BMI (±2 kg/m^2), and EWL (±5%). Baseline and 1-year lipid profile, its variation and percentage of variation was compared between surgeries.
Results
We analysed 229 patients: 72 pairs RYGB-AGB; 47 pairs RYGB-SG; and 33 pairs AGB-SG. The median age was 41 (35–52) years and 11.8% were males. BMI at the time of surgery was 44.0 ± 4.6 and 32.1 ± 4.4 kg/m^2 at 1 year. EWL at 1 year was 64.2 ± 18.9%. There were no differences in baseline lipid profile between patients submitted to different types of bariatric surgery. At 1 year, HDL

and TG improved similarly with all surgeries. TC and LDL at 1 year decreased significantly more in patients submitted to RYGB than in weight-matched patients undergoing AGB or SG.
Conclusions
RYGB is the only bariatric surgery that reduces TC and LDL in age-, sex-, BMI-, and EWL-matched patients. All three procedures improved TG and HDL similarly when the confounding effect of weight loss is eliminated.

DOI: 10.1530/endoabs.37.EP561

EP562

Comparison of demographic and biochemical characteristics among younger and older patients with metabolic syndrome

Pelin Tutuncuoglu[1], Fulden Sarac[2], Sumru Savas[2] & Sefa Sarac[3]
[1]Department of Endocrinology and Metabolism, Atatürk Training and Research Hospital, Izmir, Turkey; [2]Department of Geriatrics Medicine, Ege University Medical Faculty, Izmir, Turkey; [3]Department of Cardiology, Atatürk Training and Research Hospital, Izmir, Turkey.

Aims
The metabolic syndrome (MetS) is a summary measure of important CVD risk factors that frequently coexist. The syndrome is evident in 20–30% of middle-aged women and has been linked to the development of CVD and diabetes. The aim of the study was to examine the differences in demographic and clinical profiles among older ($\geq$60 years) and younger ($<$60 years) patients with MetS.
Methods
The study was included 45 older (mean age 63.1$\pm$12.1 years, 25 females and 20 males) and 40 younger (mean age 42.3$\pm$9.9 years, 30 females and ten males) patients wih MetS. MetS was defined as in ATP III. Demographic and biochemical parameters were compared between groups. Insulin resistance (IR) was estimated using the homeostasis model assessment (HOMA).
Results
Among older patients, 11.9% were smokers and 9.1% informed alcohol consumption. However, 29.5% of younger patients were smokers and only 12.1% of them consumed alcohol ($P=0.05$ and $P=0.30$). Mean levels of waist circumference, systolic, diastolic blood pressures, triglyceride, and LDL-cholesterol were statistically significantly higher than those of younger patients with MetS ($P=0.001$, $P=0.01$, $P=0.001$, $P=0.02$, and $P=0.002$ respectively). Mean levels of HOMA-IR were found to be 2.3$\pm$0.9 in young and 2.7$\pm$0.02 in elderly group.
Conclusions
There are differences between older and young patients with metabolic syndrome for waist circumference, smoking, blood pressures, and lipid levels.

DOI: 10.1530/endoabs.37.EP562

EP563

The risk of future IRS among women with history of gestational diabetes

Nevin Dinccag[1], Sevda Ozel Yıldız[2], Selda Gedik[1], Cemile Idız[1], Yıldız Tütüncü[1] & Bülent Canbaz[1]
[1]Endocrinology and Metabolism Division, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey; [2]Biostatistics Department, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey.

Background and aims
The history of GDM predisposes to cardiovascular disease (CVD) in the future. The aim of this study was to evaluate risk factors predicting the development of glucose intolerance and insulin resistance syndrome (IRS) in women with history of GDM in the future.
Materials and methods
55 women who had GDM 11$\pm$2 years before were enrolled into the study. After clinical examination 75 g OGTT and inflammatory markers(hsCRP, uric acid, interleukin 6 (IL6), tumor necrosis factor alpha (TNFα), visfatin, plasminogen activated inhibitor 1 (PAI1), asymmetric dimetilarginine (ADMA), and adiponectin) was performed to evaluate of current metabolic status after a decade of delivery. Based on IDF criteria participants were classified into two groups as normal (group 1) and IRS (group 2). We evaluated the relationship between metabolic status and possible risk factors such as; age, BMI, family history of DM, poor obstetric history, HbA1c and OGTT glucose levels at diagnosis of GDM; weight gain and insulin requirement during index pregnancy. SPSS 21 was used to analyse data.
Results
51% of participants developed IRS after 10th year of delivery. No predictive factor was found except screening time, first hour glucose level at the diagnosis of GDM and insulin requirement during index pregnancy Although difference was not significantly, patients in group 2 were found to have higher BMI, much more family history of DM before pregnancy and also they put less excess weight during pregnancy. As compared inflammatory parameters between two groups; HOMA-IR, hsCRP, visfatin, IL6, and PAI1 levels were detected istatistically higher; on contrary adiponectin level was less in group 2 than group 1. And currently, 43% of all participants were found that they had at any level glucose intolerance and higher insulin levels at basal and first hour of OGTT.
Conclusion
Early screening of GDM and following the patient during gestational period is important but it's much more important to follow those individuals who had high BMI, family history of DM and high glucose at first hour of OGTT at the beginning; they should be monitored closely postpartum and at least yearly follow-up should be done based on increased risk for developing IRS and therefore CVD.

DOI: 10.1530/endoabs.37.EP563

EP564

Haematopoietic system 3 years after gastric bypass

Snezana Polovina[1], Jelena Gligorijevic[2], Mirjana Sumarac/Dumanovic[1], Pavle Gregoric[3], Aleksandra Kendereski[1], Goran Cvijovic[1], Svetlana Zoric[1], Danica Stamenkovic/Pejkovic[1], Dusan Micic[3], Danka Jeremic[1], Ana Gligic[1], Aleksandra Divnic[1] & Dragan Micic[1]
[1]Clinic for Endocrinology, Diabetes and Diseases of Metabolism, Clinical Center of Serbia, Belgrade, Serbia; [2]Dietary Unit, Clinical Center of Serbia, Belgrade, Serbia; [3]Emergency Center, Clinical Center of Serbia, Belgrade, Serbia.

Bariatric surgery, especially malapsorptive procedures like gastric bypass, can lead to anaemia due to lack of iron absorption as well as vitamins essential for the normal functioning of the hematopoietic system.
Methods
We have analysed changes in red blood cells (RBC), haemoglobin (Hb), white blood cells (WBC), serum iron (Fe), and vitamin B12 3 years after gastric bypass in 142 morbidly obese patients (female, $n=108$ and male, $n=34$). All patients were on oral supplementation with 100 mg of iron and 200–400 mg of folic acid after surgery as well as 2500 µg of OHB12, i.m. injections every 3 months.
Results
Before surgery average BMI was 43.9 kg/m^2 and 3 years after BMI was 30.5 kg/m^2 ($P<0.001$). Change in number of RBC was nonsignificant (4.65.9$\pm$1.31$\times10^{12}$/l vs 4.42$\pm$1.12$\times10^{12}$/l; $P>0.05$) before and after surgery. There was no difference in Hb concentration between two measurements (137.9$\pm$15.5 g/l vs 128.9$\pm$16.3 g/l; $P>0.05$). Number of WBC was lower after surgery (10.7$\pm$3.2$\times10^9$/l vs 5.7$\pm$1.3$\times10^9$/l) with significance: $P>0.001$, but among reference range. Serum iron level increased after surgery but that was not significant (11.4$\pm$1.3 µmol/l vs 13.03$\pm$1.8 µmol/l; $P>0.05$). Vitamin B12 level remained within normal range 3 years after gastric bypass (922.5$\pm$212.2 pmol/l vs 866.7$\pm$201.1 pmol/l; $P>0.05$) without difference.
Conclusion
Even gastric bypass as malapsorptive bariatric procedure, can lead to anaemia, adequate supplementation of iron, folic acid and vitamin B12, after surgery, may prevent anaemia and vitamins essential for haematopoietic system deficiency during 3 years follow-up period.

DOI: 10.1530/endoabs.37.EP564

EP565

Patients with acute coronary syndrome have lower testosterone then healthy controls

Adriana Bednárová, Martin Kužma & Juraj Payer
5th Department of Internal Medicine, Faculty of Medicine, Comenius Univeristy and University Hospital, Bratislava, Slovakia.

Objective
Several studies report the association of low testosterone with ischaemic heart disease although the results are inconsistent. In our study we tried to evaluate the relationship between sex hormones and incidence of acute coronary syndrome (ACS).

Methods
This was a cross-sectional study. In 111 subjects (69 patients with ACS and 42 age-matched controls) we measured total testosterone, estradiol, SHBG, FSH, and LH by electrochemiluminiscence and calculate free androgen index (FAI). Patients with cancer, antiandrogen or testosterone treatment were excluded. In all patients we examined risk factors of myocardial infarction (hypertension, diabetes mellitus, dyslipidaemia, smoking, waist circumference, and BMI). Results were correlated by unpaired *T*-test and linear regression in SPCC system. In all subjects quartile analysis according to testosterone levels was performed.
Results
Patients with ACS have lower total testosterone levels comparing with controls (12.37 nmol/l vs 15.66 nmol/l, $P=0.009$). Patients had also lower levels of FAI and higher levels of FSH and LH but these were not significant. There was no difference in estradiol levels between the groups. In linear regression model testosterone correlated with waist circumference ($R^2=0.082$, $P=0.002$) and weight ($R^2=0.076$, $P=0.002$). In quartile testosterone analysis patients with testosterone levels in the lowest quartile had significantly higher incidence of ACS comparing with patients in the highest quartile (RR 1.72, CI 1.1; 2.6). Patients in the lowest testosterone quartile had also higher incidence of diabetes mellitus, dyslipidaemia, hypertension, and smoking.
Conclusions
Patients with ACS have significantly lower total testosterone levels and inversely, patients in the lowest testosterone quartile have higher incidence of ACS. Testosterone level correlates significantly with weight and waist circumference. Low testosterone is strongly associated with adiposity in patients with ACS and probably plays a role in metabolic syndrome.

DOI: 10.1530/endoabs.37.EP565

EP566

HLA and metabolic parameters that define obesity in Amerindians for the first time

Antonio Arnaiz-Villena, Cristina Areces, Mercedes Enríquez-de-Salamanca, Ester Muñiz, Narcisa Martínez-Quiles, José Manuel Martín-Villa, Pablo Vargas & Diego Rey
University Complutense, Madrid, Spain.

Metabolic syndrome and obesity are principal causes of morbidity all over the world, particularly for their association to cardiovascular risk. There is now an obesity worldwide epidemic (Globesity). Amerindians are often living in countries and remote areas with unavailable sophisticated diagnoses methodologies. However, waist circumference is a reliable and easy to record parameter of visceral obesity and MS. Waist circumference normal values are not yet established in Amerindians: South Asian and Japanese values have been recommended for Amerindian use. The purpose of this study is to objectively determine for the first time the waist circumference measure cut-off points for Amerindians, by using i) HLA phenotype to ensure that population tested is Amerindian and ii) measurement of biochemical markers which were diet independent. A total of 303 unrelated Amerindian adults recently immigrated to Madrid were studied; they were healthy, since they were questioned and tested as appropriate for blood donation and recent weight increase. Waist circumference was measured in these voluntary blood donors after written consent. Chosen subjects for study had HLA quasi-specific Amerindian genes. Amerindians with type 1 or 2 diabetes or family antecedents were removed from the study. A receiver operating characteristic analysis was used to compare the predictive validity and to find out the optimal cut-off points of waist circumference normal values. Cut-off points were $\leq$88.5 cm in males and $\leq$82.5 cm in females. Obtained waist circumference values recorded here in normal Amerindians are different to the previously recommended ones: those of South Asians. In addition, PPARγ and adiponectin gene linkage to obese Amerindians was not observed. These parameters may be of great value for Spain and American countries for establishing preventive programs in order to predict and control metabolic syndrome.

DOI: 10.1530/endoabs.37.EP566

EP567

Does the presence of obesity and/or metabolic syndrome affect the course of acute pancreatitis?

Samer Al-Sawalhi & Hamdi Al-Maramhy
Taibah University, Al-Madina, Saudi Arabia.

Objective
The incidence of acute pancreatitis (AP) is rising with increased prevalence of obesity, which exacerbates pancreatic injury. Metabolic syndrome (MS) is defined as a cluster condition of cardiovascular risk factors, including hyperglycaemia, dyslipidaemia, hypertension, and central obesity. We analysed if the presence of obesity and/or MS affects the course of pancreatitis.
Methods
Data were collected from 140 patients with AP between January 2010 and February 2013. Anthropometric data, including BMI and waist circumference, were measured. Biochemical tests were used including fasting glucose, triglyceride, LDL and HDL cholesterol levels, and total cholesterol level. Atlanta criteria, Acute Physiology and Chronic Health Evaluation II, and Ranson scoring system were used to define severe AP. Patients were classified as having MS based on the International Diabetic Federation criteria.
Results
The mean BMI was 30.15 kg/m^2. Sixteen (11.4%) patients had severe AP, whereas 124 (88.6%) patients had mild AP. We found that 62.8% of patients with AP fulfilled the criteria of MS ($P=0.000$). Body weight can be used to predict clinical severity of AP with significant P value $=0.009$.
Conclusions
The presence of MS in patients with pancreatitis is noticeable, but it does not affect the course of disease severity, whereas obesity correlates with pancreatitis severity.

DOI: 10.1530/endoabs.37.EP567

EP568

Gender-related risk of cardiovascular diseases in patients with type 2 diabetes mellitus

Lev Prystupiuk, Oleksandr Prystupiuk & Marianna Naumova
Bogomolets National Medical University, Kyiv, Ukraine.

Introduction
The main causes of death in the world today is non-communicable diseases (NCDs). A research of the World Bank found out that 82% of deaths in Ukraine are caused by chronic NCDs, 3.6% of which compose diabetes mellitus. And since the course of type 2 diabetes mellitus (T2DM) is usually long, it requires special, costly medical care for significant period of patient's lifetime.
Materials and results
Our research involved 592 males and 1170 females with T2DM. We determined BMI, glycaemia, total cholesterol, HDL-C, and non-HDL-C. Dyslipidaemia is established with cholesterolaemia over 5.20 mmol/l and with HDL-C under 1.02 mmol/l in males and under 1.29 mmol/l in females. In our study group, cholesterol level in men was 6.41 ± 0.03 mmol/l in women – 6.23 ± 0.01 mmol/l ($P<0.05$), while HDL-C was respectively 1.89 ± 0.88 and 1.88 ± 0.07 mmol/l ($P<0.05$), and non-HDL-C – 4.60 ± 0.02 and 3.38 ± 0.05 mmol/l ($P<0.05$). Patients were divided, according to cholesterolaemia, into the following groups: under 5.3, 5.3–6.5, and over 6.5 mmol/l. In relation to this, males were the following percentages: 38, 57, and 5%; females: 28, 64, and 8%. Regarding fasting glycaemia, patients' groups were: under 6.2, 6.2–7.8, and over 7.8 mmol/l. Accordingly, cholesterol level related to glycaemic groups in men was 5.70 ± 0.01, 5.90 ± 0.05, and 5.99 ± 0.04 mmol/l ($P<0.001$) and in women: 4.86 ± 0.03, 6.50 ± 0.03, and 7.50 ± 0.03 mmol/l ($P<0.001$) respectively. In accordance with BMI we had the following classification: normal weight, overweight, obesity. And male patients' cholesterol was respectively as follows: 5.81 ± 0.06, 6.12 ± 0.04, and 6.10 ± 0.05 mmol/l, while female cholesterol: 5.48 ± 0.04, 5.56 ± 0.02, and 5.77 ± 0.01 mmol/l.
Conclusions
i) Atherogenic dyslipidemia in 70% of patients with T2DM of both sexes is caused by an increase in blood non-HDL-C. ii) Atherogenic dyslipidaemia correlated with the state of compensation of diabetes and body weight. iii) Therapeutic correction of dyslipidaemia in patients with T2DM should be normalization of blood glucose and body weight.

DOI: 10.1530/endoabs.37.EP568

EP569

Effect of obesity and diabetes mellitus type 2 on vascular stiffness

Olga Bourko[1], Tatiana Netchessova[1], Irina Bourko[2], Larisa Danilova[2], Elena Dashkevich[2] & Galina Korolenko[2]
[1]Republican Scientific and Practical Center Cardiology, Minsk, Belarus; [2]Belarusian Medical Academy of Postgraduate Education, Minsk, Belarus.

Aim
To investigate the impact of overall obesity (Ob) and diabetes mellitus type 2 (DM2) on arterial stiffness and degree of insulin resistance in patients with arterial hypertension (AH) and abdominal Ob (AOb).
Design and method
74 subjects were divided according to presence of AH, AOb, Ob, and DM2 without insulin therapy. Control group 1 consisted of 26 subjects without AH, AOb, Ob, and DM2. All patients with AH were also diagnosed with AOb and amounted to 48 subjects. Then patients with AH and AOb were divided into two groups (groups 2 and 3 respectively) according to presence of Ob, defined by BMI and furthermore, DM2. Carotid-femoral pulse wave velocity (PWVc-f) measurements were performed using SphygmoCor. Homeostasis model assessment-insulin resistance (HOMA-IR) was calculated by the following formula: fasting plasma insulin (mU/ml) × fasting plasma glucose (mmol/l)/22.5.
Results
In the group comparison by BMI: PWVc-f and HOMA-IR increased consistently from groups 1 to 3. PWVc-f was significantly higher in hypertensive patients with AOb and Ob than in hypertensive patients with AOb and without Ob (PWVc-f = 8.69 ± 1.8 and PWVc-f = 7.43 ± 1.3; $P < 0.05$). HOMA-IR did not show significance. In the group comparison by presence of DM2: PWVc-f and HOMA-IR increased consistently from groups 1 to 3. PWVc-f and HOMA-IR were significantly higher in hypertensive patients with AOb and DM2 than in hypertensive patients with Aob and without DM2 (PWVc-f = 9.5 ± 1.8 and PWVc-f = 7.71 ± 1.5, $P < 0.001$; and HOMA-IR = 7.09 ± 3.54 and HOMA-IR = 2.83 ± 1.2; $P < 0.001$). Significant differences between groups persisted after adjustment for age, sex, and BMI.
Conclusions
Presence of overall Ob together with AOb had a significant adverse effect on arterial stiffness in patients with AH both men and women. This adverse effect is similar with impact of DM2 on arterial stiffness in patients with AH together with AOb. Measurement of PWVc-f showed higher significance vs HOMA-IR measurements in the study groups.

DOI: 10.1530/endoabs.37.EP569

EP570

Metabolism of sphingolipids in experimental obesity and insulin resistance

Talat Saatov[1], Bakhodyr Zainutdinov[1], Elvira Ibragimova[1], Sanobar Irgasheva[1], Akmaral Tashmanova[2] & Mukhamadjon Mustafakulov[1]
[1]Institute of Bioorganic Chemistry, Uzbekistan Academy of Sciences, Tashkent, Uzbekistan; [2]Uzbekistan Ministry of Education, Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan.

Sphingolipids constitute the structural base for all types of biological membranes, and are numerous in human and animal tissues. Metabolites of sphingolipids act as biological effectors, modulators and mediators in a number of biochemical processes; they are known to be pathogens in various human pathologies.
We aimed at studying activity of sphingomyelinase, concentrations of sphingomyelin and its metabolites, such as ceramide and sphingosine, in organs of rats with experimental diabetes.
Experimental model of obesity and insulin resistance was used to study activity of sphingomyelinase, and concentrations of sphingosine and ceramide. As compared with the controls, in the liver of experimental animals activity of neutral and acid sphingomyelinase was found to increase by 25 and 21% respectively. In skeletal muscles of obese animals, activity of neutral and acid sphingomyelinase increased by 45 and 70% respectively. The findings can be the evidence for stimulation of sphingomyelinase activity in the liver and skeletal muscles in rats with experimental obesity. Significant alterations in the content of sphingomyelin and its metabolites were observed in obese rats; these alterations were found to be oppositely directed. In the liver of obese rats, sphingomyelin was found to decrease by 25%; while in skeletal muscles its concentration decreased more than by 31%. Concentrations of ceramide and sphingosine in the liver of obese rats were found to increase by 15 and 23%, respectively, as compared with the controls. In skeletal muscle of obese rats, concentrations of ceramide and sphingosine increased by 19 and 68% respectively.
We have established increase in the activity of sphingomyelinase and accumulation of ceramide and sphingosine, metabolites of sphingomyelin, in the liver and skeletal muscles of rats with experimental obesity and insulin resistance. Ceramide overproduction plays a key role in the onset and development of insulin resistance.

DOI: 10.1530/endoabs.37.EP570

EP571

Adiponectin response to vegetarian diet is gender-dependent and inversely related to uric acid

Marijana Vučić Lovrenčić[1], Iva Košuta[1], Marko Gerić[2], Goran Gajski[2] & Verica Garaj Vrhovac[2]
[1]Merkur University Hospital, Zagreb, Croatia; [2]Medical Research and Occupational Health, Zagreb, Croatia.

Introduction
Beneficial influence of vegetarian dietary habits in reducing common risk factors of metabolic syndrome has been recently evidenced. However, adiponectin production and secretion has been scarcely studied in vegetarians, despite its important potential in recovering metabolic homeostasis by reducing inflammation and insulin resistance.
The aim of this study was to evaluate the influence of vegetarian diet on serum adiponectin levels and it's association to the established inflammatory and metabolic biomarkers.
Methods/design
Total serum adiponectin (ADN), leukocytes (L), CRP, plasma glucose (PG), insulin (INS), and uric acid (UA) were measured in healthy, non-obese, age-matched vegetarian ($n = 40$; M/F = 16/24) and omnivore subjects ($n = 39$; M/F = 15/24). HOMA-2 model was used for the assessment of β-cell function (BS), insulin sensitivity (IS), and insulin resistance index (IRI).
Results
Serum ADN levels were significantly higher in female vegetarians than the respective omnivore controls (14.2 ± 5.82 mg/l vs 10.82 ± 3.29 mg/l; $P = 0.017$), whereas no dietary-associated difference was observed in male vegetarian and omnivore subjects respectively (6.87 ± 2.57 mg/l vs 6.74 ± 3.07 mg/l; $P = 0.898$). Stepwise multiple regression analysis identified uric acid as the significant negative determinant of ADN in vegetarians ($r_{partial} = -0.4585$, $P = 0.002$), while in omnivore subjects only BMI was found to be significantly associated to ADN levels ($r_{partial} = -0.4439$, $P = 0.016$). In comparison to controls, significantly lower INS (47.6 ± 19.2 pmol/l vs 57.7 ± 23.7 pmol/l; $P = 0.042$) and IRI (1.01 ± 0.42 vs 1.22 ± 0.49; $P = 0.041$), as well as higher BS ($115.5 \pm 42.9\%$ vs $94.2 \pm 35.3\%$; $P = 0.019$) were found in vegetarians.
Conclusion
Vegetarian dietary habits result into improved insulin sensitivity and β-cell function. Gender diversity in adiponectin response and inverse association to uric acid indicate distinct effects of vegetarian diet to adipose tissue metabolism.
Disclosure
This work was supported by the Croatian Ministry of Science, Education and Sports (grant numbers 022-0222148-2125 and 045-1191348-0139).

DOI: 10.1530/endoabs.37.EP571

EP572

Fibrate therapy predispose to influenza vaccine-induced rabdomyolysis

Goknur Yorulmaz[1], Hatice Hamarat[2], Emel Gonullu[3] & Ayse Ekim[4]
[1]Endocrinology Department, Eskisehir State Hospital, Eskisehir, Turkey; [2]Internal Medicine Department, Eskisehir State Hospital, Eskisehir, Turkey; [3]Rheumatology Department, Eskisehir State Hospital, Eskisehir, Turkey; [4]Department of Physical Medicine Rehabilitation, Eskisehir State Hospital, Eskisehir, Turkey.

Introduction
Fibrates are widely used to manage dyslipidemia but these drugs can induce rhabdomyolysis with acute renal failure. Rhabdomyolysis is a skeletal muscle cell damage condition associated with the release of toxic components of the cells and to the end;renal failure. The onset of rhabdomyolisis can extend to 6 months with fibrate therapy. Some researchers purpose that the influenza vaccıne can induce the rhabdomyolisis in patients who receive myotoxic drugs.Here we present a case who develops rhabdomyolisis and acute renal failure after influenza vaccine during fibrate therapy.
Case
A 65-year-old male patient admitted to the hospital with weakness and pain of the extremity muscles. He had tenderness widespread of the body and feel difficulty to move. He had coronary heart disease and hyperlipidemia. He was taking 267 mg of fenofibrate daily for 5 months and had influenza vaccine administration a week before admission to the hospital. Laboratory examination showed markedly elevated serum creatine kinase levels (27 730 U/l) and creatinine was

2.16 mg/dl (creatinine level was normal range before the vaccine administration). After discontinuing the fibrate therapy and adequate fluid resuscitation renal function recovered and the symptoms of myopathy resolved.
Conclusion
The risk of rhabdomyolysis increases with polypharmacy with myotoxic agents like lipid lowering medications. Also influenza vaccination administration must keep in mind an another myotoxic situation especially during lipid lowering drugs like fenofibrate.

DOI: 10.1530/endoabs.37.EP572

EP573

Outcomes of gastric bypass for morbid obesity after 5-year follow-up

María Belén Ojeda-Schuldt[1], Isabel Mateo-Gavira[1], Francisco Javier Vilchez-López[1], María Ángeles Mayo-Osorio[2], José Manuel Pacheco-García[2], Luis Escobar-Jiménez[1] & Manuel Aguilar-Diosdado[1]
[1]Department of Endocrinology, University Hospital Puerta del Mar, Cádiz, Spain; [2]Department of Surgery, University Hospital Puerta del Mar, Cádiz, Spain.

Introduction
Currently, there are few data on long-term effects of bariatric surgery. We present the results of 5-year follow-up of a cohort of patients with gastric bypass surgery (GBP).
Objectives
i) To determine the prevalence of major comorbidities of morbid obese; ii) to evaluate the gastric bypass effect on this comorbidities, and 10-year estimated cardiovascular risk after 5-year follow-up; and iii) to assess the impact of bariatric surgery on the quality of life in these patients.
Methods
Prospective analysis in a cohort of 124 patients with morbid obesity who underwent bypass surgery. Demographic and anthropometric parameters, 10-year risk for coronary heart disease (estimated by Framingham risk score), complications from surgery and quality of life through Bariatric Analysis and Reporting Outcome System (BAROS) test were analysed before surgery and during follow-up.
Results
A total of 124 patients, who underwent surgery between 2005 and 2009, where included. The mean age was 37.88 ± 10.29 years, 76.6% were women and the mean preoperative BMI was 51.71 ± 7.35 kg/m^2. At 2 and 5 years of follow-up, remains a BMI of 30.48 ± 4.7 and 31.27 ± 7.08 kg/m^2 respectively. After 5 years of follow up, the percentage of weight lost was 68.31%. Remission of hypertension, dyslipidemia, and diabetes mellitus type 2 had occurred in 89.5, 95.8, and 95.7% respectively ($P<0.001$). The Framingham risk score was reduced from 7.7 ± 9.5 to 2.8 ± 3.5% ($P<0.005$). Regarding surgical complications, 14.7% showed early complications and 29% late complications. BAROS test was successful in 95% of cases.
Conclusions
In our area, outcomes from gastric bypass in obtaining weight lost and resolution of comorbidities after 2 years of surgery also remains at 5-year follow up with a minimum rate of surgical complications.

DOI: 10.1530/endoabs.37.EP573

EP574

The prevalence of obesity and metabolic syndrome among inpatients at a Forensic Psychiatric Hospital in the Republic of Ireland

Arimin Mat[1], Tomas Ahern[2], Tracey Hoare[3], Paul McCarran[3], Harry G Kennedy[3,4] & Donal O'Shea[1,2]
[1]Weight Management Service, St Columcilles Hospital, Loughlinstown, Ireland; [2]Department of Endocrinology, St Vincent's University Hospital, Dublin 4, Ireland; [3]National Forensic Mental Health Service, Central Mental Hospital, Dublin 14, Ireland; [4]Department of Psychiatry, Trinity College, Dublin 8, Ireland.

Introduction
Patients in secure forensic psychiatric units are at high risk of developing obesity due to complex interplay of factors including antipsychotic medications, restrictions on freedom and poor motivation to healthy lifestyle and physical activities.
Aim
To establish the prevalence of obesity and metabolic syndrome (MetS) in a secure forensic psychiatric hospital in the Republic of Ireland (ROI).
Methods
We carried out a longitudinal study in the National Forensic Mental Health Service in the (institution name, four words), Dublin. National Cholesterol Educational Program, Adult Treatment Panel III (NCEP/ATP III) definition was used to diagnose MetS.
Results
Number of patients was 76 (males = 68 (89.5%)). Mean age was 44.7 years (s.d. = 13.4). All patients were on long-term antipsychotics. Duration of admission was longer in males (9.6 years (s.d. = 10.5) vs 3.8 (s.d. = 2.9) in females, $P=0.1232$), mean was 9.2 (s.d. = 10.2). Mean weight at admission was 90.2 kg (s.d. = 17.7), BMI = 30.0 kg/m^2 (s.d. = 5.9); this increased at time of study (TOS) to 98.3 kg (s.d. = 17.9, $P=0.006$), BMI = 32.8 (s.d. = 6.1, $P<0.001$). Average weight gain was 8.1 kg. At admission, 24 (31.6%) patients were overweight and 35 (46.0%) were obese; at TOS, 9 (11.8%) were overweight and 57 (75%) were obese ($P<0.001$). Twenty-nine (37.2%) patients met the criteria for MetS at admission, 44 (56.6%) at TOS (the additional 15 met the criteria solely due to weight gain). Three had diabetes at admission, 12 (15.8%) at TOS ($P=0.012$).
Conclusion
We conclude that obesity and MetS are highly prevalent in our centre. Given that obesity is a significant contributor to MetS and its complications, patients in forensic institutions such as this should receive appropriate weight management programme from time of admission. Urgent investment in dietetic and physiotherapy service is needed.

DOI: 10.1530/endoabs.37.EP574

EP575

Can obese patients on antipsychotic medications achieve weight loss in an unmodified general population lifestyle-intervention weight management programme?

Arimin Mat[1], Tomas Ahern[2], Cathy Breen[1], Colin Dunlevy[1] & Donal O'Shea[2]
[1]Weight Management Service, St Columcille's Hospital, Loughlinstown, Ireland; [2]Department of Endocrinology, St Vincent's University Hospital, Dublin 4, Ireland.

Background
Many antipsychotics are obesogenic and contribute to significant weight gain with serious implications on patients' physical and mental well-being. However, patients on antipsychotics are often excluded from unmodified lifestyle-intervention weight management programmes and trials.
Objectives
To determine if weight loss is possible for antipsychotic-medicated obese patients when enrolled in an unmodified lifestyle-intervention weight management programme.
Methods
Data from 44 antipsychotic-medicated participants (AP) and 88 matched control participants (CP) were analysed to determine weight outcomes. Dietary and activity behaviours at baseline for an AP sub-cohort were also reported. Results were expressed as mean (95% CI); Mann–Whitney U test was used to assess differences between cohorts.
Results
Enrolment mean weight of AP was 139.8 kg (130.5–149.0 kg) compared with CP of 140.5 kg (134.4–146.6 kg; $P=0.478$). Enrolment BMI was 49.1 kg/m^2 (46.0–52.3) compared with 48.9 kg/m^2 (46.8–51.1; $P=0.515$). Twenty-five AP participants lost weight (mean weight loss: -9.1 kg). There was no difference in weight outcomes in AP compared to CP groups (-2.0 vs -2.4 kg; $P=0.824$). Also 9 (20.5%) AP participants lost 5% baseline weight compared with 18 (20.5%) in CP ($P>0.99$) while 5 (11.4%) in AP lost 10% weight compared with 6 (6.8%) in CP ($P=0.373$). At baseline, the AP group ate fast food 1.7 ± 1.2 times/week, fresh fruit 1.0 ± 1.4 times/day and reported 2.5 ± 3.0 missed breakfasts/week. Baseline gait speed was lower in AP group (0.99 ± 0.2 m/s vs 1.09 ± 0.34 m/s in CP cohort) and improved slightly to 1.01 ± 0.3 m/s.
Conclusion
Modest weight loss can be achieved in patients on long-term antipsychotics enrolled into an unmodified weight management programme designed for the general population. Typical dietary strategies such as encouraging breakfast

consumption and reducing fast food and increased physical activities are relevant to this cohort of patients.

DOI: 10.1530/endoabs.37.EP575

EP576

Factors affecting gender differences in the association between health-related quality of life and metabolic syndrome components: Tehran Lipid and Glucose Study (TLGS)

Parisa Amiri[1], Tina Deihim[1], Reza Taherian[1], Mehrdad Karimi[1,2], Safoora Gharibzadeh[2,3], Mohammad Asghari-Jafarabadi[4] & Fereidoun Azizi[3]

[1]Research Institute for Endocrine Sciences, Research Center for Social Determinants of Health and Obesity Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [2]Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran; [3]Research Institute for Endocrine Sciences, Endocrine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [4]Faculty of Health and Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran.

Introduction

Gender differences in the association between health-related quality of life (HRQoL) and metabolic syndrome (MetS) have been studied by previous researches. This study aimed to assess influential factors causing gender differences between HRQoL and MetS components using structural equation modelling.

Methods

A sample of 950 adults from TLGS were recruited in this study between 2005 and 2007. Health-related quality of life was assessed using the Iranian version of SF-36. Structural equation modelling was applied to determine the relationships between the constructs of MetS components (MetSCs) and HRQoL within the gender groups.

Results

Based on the primary hypothesis, MetSCs, physical and mental HRQoL were fitted in a model (χ^2/df = 1.52, RMSEA = 0.023, CFI = 0.98, and GFI = 0.97). The adjusted negative effect of MetSCs on physical HRQoL was significant only in women. The proportion of all the cardio-metabolic risk factors as well as physical domain subscales were higher in women ($P<0.05$). Among socio-behavioural factors, physical activity in both men ($\beta=3.19$, $P<0.05$) and women ($\beta=3.94$, $P<0.05$), age ($\beta=-3.28$, $P<0.05$) and education ($\beta=2.68$, $P<0.05$) just in women and smoking ($\beta=2.28$, $P<0.05$) just in men directly affected physical HRQoL. Regarding the mental domain, physical activity ($\beta=3.37$, $P<0.05$) and marital status ($\beta=3.44$, $P<0.05$) in women and age ($\beta=2.01$, $P<0.05$) in men were direct effective factors. While age and smoking had a sex-specific indirect effect on the association between physical HRQoL and MetSCs, none of the socio-behavioural factors was found to have a direct effect on this association between men and women significantly.

Conclusion

Structural differences of physical HRQoL and MetSCs as well as different influential patterns of socio-behavioural factors specifically age and smoking seems to have a pivotal role to create this gender differences. Although, the proportion of SBP, WC and bodily pain were the highest in both genders, except for DBP, all the cardio-metabolic risk factors and physical subscales had significant higher proportion in women.

DOI: 10.1530/endoabs.37.EP576

EP577

Secondary prevention after acute coronary syndrome in patients with type 2 diabetes: results from a routine clinical practice

Manuel Cayón Blanco, Ana Del Río Lechuga, Carolina García-Figueras Mateos & Patricia Rubio Marín

Hospital SAS Jerez de la Frontera, Andalusia, Spain.

Rationale

Secondary prevention of coronary artery disease (CAD) in patients with type 2 diabetes mellitus (T2DM) has shown benefit but the level of control is still disappointing. Most of the results are documented within clinical trials. There isn't enough information in routine clinical practice at short-term tracing. The main aim of this study is to collect information about the level of control of major risk factors in non-selected patients.

Methods

Observational and retrospective study. Patients with T2D who had suffered myocardial infarction between January and December 2012 were included. Data provided by clinical history, with special regard to major cardiovascular risk factors were recorded. Optimal control of risk factors was defined by current clinical guidelines. Clinical events and achievement of targets at baseline, 6 months and 1 year after coronary event were recorded.

Results

Data from 48 T2DM patients (47.9% females, mean age: 70.6 ± 8.7 years, and mean diabetes duration: 10.9 ± 9 years) were collected. 79.2% had hypertension and 66.7% had hyperlipidaemia. At baseline, proportion of patients who met target for non-smoking, SBP, LDL-C, and HbA1c was 89.6, 62.2, 40, and 22.2% respectively. The rates of patients with adequate control at 6 and 12 months after discharge were as follows: non-smokers: 93.9 and 97.1% ($P=0.01$); SBP: 74.4 and 71.4% ($P=0.004$); LDL-C: 70 and 83.3% ($P<0.001$), and HbA1c: 41.4 and 35.5% ($P=$not significant). Although, follow-up HbA1c level was lower than at baseline, no significantly difference was observed (7.9 ± 1.3% vs 7.3 ± 1.2% vs 7.3 ± 2.1%; $P=0.06$).

Conclusions

Our outcomes from a routine clinical practice are relatively poor and don't differ much from the trials results. The rate of adequate control for each risk factor was similar at 6 months and at 1-year after coronary event. It reflects that there is an early improvement that is maintained after optimising treatment.

DOI: 10.1530/endoabs.37.EP577

EP578

A 5-year review of the metabolic changes after laparoscopic sleeve gastrectomy among obese Hong Kong Chinese in a regional hospital

Cheuk Wah Ho, Grace Kam & Man Wo Tsang

United Christian Hospital, Hong Kong, China.

Background and aims

Obesity is a global problem. Laparoscopic sleeve gastrectomy (LSG) was introduced in our hospital since 2008. This study aimed at reviewing the metabolic changes after LSG among Hong Kong Chinese in a regional hospital.

Materials and methods

47 patients who received LSG in our hospital from June 2008 to October 2012 were retrospectively reviewed. Change in body weight (BW) and glycaemic control up to 5 years were evaluated. Rate of remission of diabetes at 1 year after operation was also reviewed. Statistical method used include Wilcoxon's signed rank test for paired-related groups and Mann–Whitney *U* test for paired non-related groups.

Results

The mean age was 43.7 (19–63) years. The mean baseline BW and BMI were 105.7 ± 3.5 and 39.7 ± 4.6 kg/m^2 respectively. The maximum weight loss was achieved at post-operative 1 year, i.e. 25.1 ± 1.7 kg (23.7 ± 1.49%) ($P=0.00$). Significant % weight loss was still maintained at post-operative 5 years i.e. 21.9 ± 1.39% ($P=0.011$, $n=9$). For diabetic patients, the improvement in diabetic control was already shown before maximum weight loss. The greatest improvement in fasting blood glucose (FBG) was seen at 1 month dropping from 7.8 ± 0.6 to 6.2 ± 0.5 mmol/l ($P=0.00$). The HbA1c reduced from baseline of 7.9 ± 0.4 to 6.7 ± 0.3% at 3 months ($P<0.05$). At 1 year after operation, patients achieving remission of diabetes showed statistically significant greater % weight loss (24.9 ± 1.3% vs 17.6 ± 3.6%), lower baseline FBG (6.1 ± 0.2 mmol/l vs 10.2 ± 1.0 mmol/l) and shorter duration of diabetes (2.7 years vs 9.6 years) All diabetic patients who were on diet control before operation achieved remission while the rate for those on oral anti-diabetic drugs and insulin were 58.3 and 27.2% respectively. Remission of diabetes was defined as FBG <7 mmol/l and HbA1c <6.5% without medication.

Conclusion

LSG showed sustainable weight loss 5 years after operation. Characteristics of patients achieving remission of diabetes were evaluated which helped to predict outcome.

DOI: 10.1530/endoabs.37.EP578

EP579

Malignant tumours in patients with type 2 diabetes mellitus and obesity

Siarhei Shymanets[1,2], Larisa Danilova[2], Maxim Lushchik[2], Vyacheslav Dudarev[1,2], Andrey Karman[1], Siarhei Kharuzhyk[1] & Veronika Dovgalo[1]
[1]N.N. Alexandrov National Cancer Centre of Belarus, Minsk District, Belarus; [2]Belarusian Medical Academy of Post-Graduate Education, Minsk, Belarus.

Backgrounds and aim
Epidemiologic evidence suggests that people with diabetes are at significantly higher risk for many forms of cancer. The aim of the research was to identify cancer incidence distribution in Belarusian patients with type 2 diabetes mellitus.
Methods
The study group included 73 patients: 46 (63%) women (mean age 65 ± 8 years) and 27 (37%) men (70 ± 7 years) with concurrent diabetes and cancer treated at Alexandrov National Cancer Centre of Belarus in 2013. The mean time of type 2 diabetes mellitus course before cancer diagnosis was 7.8 ± 5.8 years. A meaningful associations between diabetes and cancer incidence in men and women subgroups were analysed.
Results
Among women breast cancer was the leading malignancy, accounting for 59% (27 patients), corpus uteri cancer mentioned in 15% (seven patients), cervix in 7% (three patients), lung in 4% (two patients), and other localizations occurred in 15% (seven patients). In men subgroup the higher incidence were registered for lung and prostate cancers, accounting 22% (six cases) and 19% (five cases) accordantly, stomach cancer revealed in 15% (four persons), bladder 11% (three persons), kidneys 7% (two persons), and other localisations 26% (seven persons). Multiple primary malignancies were diagnosed in 18% (ten women and three men). The most frequent initial cancer types were women breast (five patients), lung (two patients), and corpus uteri (two patients), the other types made stomach, colon, cervix uteri cancer, and myeloleucosis.
Conclusion
Breast cancer was the predominated neoplasm (59%) in women with diabetes mellitus. The most common cancer in males was lung cancer (22%) and prostate cancer (19%). 18% of the patients with type 2 diabetes mellitus had multiple primary malignancies. Future researches are needed for better understanding of possible biologic links between diabetes and cancer risk.

DOI: 10.1530/endoabs.37.EP579

EP580

Preoperative endocrinological evaluation of patients apply for bariatric surgery

Ilkay Cakir[1], Yasin Simsek[2], Riza Kutanis[3], Serkan Menekse[4], Emine Isil Ustun[5] & Dede Sit[6]
[1]Department of Endocrinology, Bagcilar Research and Education Hospital, Istanbul, Turkey; [2]Department of Endocrinology, Hitit University Hospital, Çorum, Turkey; [3]Department of General Surgery, Bagcilar Research and Education Hospital, Istanbul, Turkey; [4]Department of Oncology, Bagcilar Research and Education Hospital, Istanbul, Turkey; [5]Department of Physical Therapy, Bagcilar Research and Education Hospital, Istanbul, Turkey; [6]Department of Internal Medicine, Bagcilar Research and Education Hospital, Istanbul, Turkey.

Introduction
Since bariatric surgery is considered to be a more effective treatment modality for morbid obesity, a growing number of patients have been referred to endocrinology clinics in order to exclude an underlying cause. Routine preoperative testing to screen Cushing's syndrome (CS) or hypothyroidism is still debatable. The aim of this study is to evaluate the accuracy of routine testing in preoperative endocrinological evaluation.
Methods/design
Clinical files of 164 patients who applied for bariatric surgery to our outpatient clinic between January 2014 and January 2015 were reviewed. Cortisol levels following low-dose dexamethasone administration, and free thyroxine, TSH were measured to exclude CS and hypothyroidism respectively. Serum cortisol <1.8 μg/dl was the cut-off point for normal suppression. We also have measured HbA1c, insülin, and fasting glucose as a part of our pre-surgical protocol. HOMA-IR was used to determine insulin resistance.
Results
One hundred and sixty-four patients (43 men and 121 women) with a mean age of 39.96 ± 10.95 years and a mean BMI of 49.50 ± 34.36 kg/m^2 were reviewed. Only in one patient pseudo CS was considered. Primary subclinical hypothyroidism was 12% and primary subclinical hyperthyroidism was 1%, while 151 patients were euthyroidic (92%). The prevalence of known diabetes mellitus was 26%. No new patient of diabetes mellitus was diagnosed, while the prevalence of impaired fasting glucose was 38%. Mean HOMA-IR levels were 5.94 ± 3.5 and mean HbA1c levels were 5.6 ± 0.4% when previously known diabetics were excluded.
Conclusion
Routine screening for CS, hypothyroidism seems to be not required and may cause needless expenditures for national health systems in patients who apply for preoperative evaluation for bariatric surgery. For the time being, diagnostic tests for CS and hypothyroidism in morbidly obese patients should be limited to patients who have accompanying more clinical signs and symptoms.

DOI: 10.1530/endoabs.37.EP580

EP581

Liver enzymes and triglycerides predict biomarkers of insulin sensitivity in obese, non-diabetic adult patients

Ana Gligic[1], Mirjana Sumarac-Dumanovic[1,2], Snezana Polovina[1], Aleksandra Kendereski[1,2], Danica Stamenkovic-Pejkovic[1], Goran Cvijovic[1,2], Svetlana Zoric[1], Danka Jeremic[1], Jelena Milin-Lazovic[1] & Dragan Micic[1,2]
[1]Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia, Belgrade, Serbia; [2]Faculty of Medicine, University of Belgrade, Belgrade, Serbia.

Introduction
Obesity is a risk factor for the development of insulin resistance, type 2 diabetes, cardiovascular diseases and non-alcoholic fatty liver disease. The aim of our study was to examine predictive value of liver enzymes in assessing biomarkers of insulin sensitivity in obese, non-diabetic adults.
Methods
1104 obese, non-diabetic adults were included in the study. Patients were divided into two groups: Group A (BMI 30.0–39.9 kg/m^2, $n=499$) and Group B (BMI ≥ 40 kg/m^2, $n=605$). After 12 h of fasting, anthropometric evaluation (BMI, waist-to-hip ratio and percentage body fat) was performed and blood levels of glucose, insulin, HbA1c, total cholesterol, HDL, LDL, triglycerides, AST, ALT, γ-GT and CRP were obtained. HOMA-IR was calculated. Multiple linear regression was used for statistical analysis.
Results
We found that ALT, γ-GT and triglycerides are predictors of HOMA-IR score in Group A ($R^2=0.02$, $P=0.007$; $R^2=0.04$, $P<0.001$; $R^2=0.06$, $P<0.001$, respectively), as well as in Group B ($R^2=0.03$, $P=0.002$; $R^2=0.07$, $P<0.001$, $R^2=0.04$, $P<0.001$, respectively). Percentage of body fat predicts HOMA-IR score in Group A ($R^2=0.02$, $P=0.021$), whereas waist-to-hip ratio predicts HOMA-IR score in Group B ($R^2=0.05$, $P<0.001$). Moreover, ALT and γ-GT predict HbA1c in Group B ($R^2=0.03$, $P<0.001$; $R^2=0.06$, $P<0.001$, respectively).
Conclusion
These results have verified that parameters of insulin sensitivity in obese, non-diabetic patients could be presumed mainly by levels of liver enzymes and triglycerides. Therefore, these data contribute to the essential role of liver function tests in the detection of metabolically abnormal obesity.

DOI: 10.1530/endoabs.37.EP581

EP582

Neutrophil to lymphocyte ratio as an inflammatory marker in obesity

Neslihan Soysal-Atile[1], Betül Ekiz-Bilir[1], Bülent Bilir[2], Derya Baykiz[3], Birol Topçu[4] & Murat Aydin[5]
[1]Endocrinology Department, Tekirdag State Hospital, Tekirdag, Turkey; [2]Internal Medicine Department, Namik Kemal University Faculty of Medicine, Tekirdag, Turkey; [3]Cardiology Department, Tekirdag State Hospital, Tekirdag, Turkey; [4]Biostatistics Department, Namik Kemal University Faculty of Medicine, Tekirdag, Turkey; [5]Biochemistry Department, Namik Kemal University Faculty of Medicine, Tekirdag, Turkey.

Aim
Cardiovascular morbidity and mortality of obesity is associated with classic risk factors, namely dyslipidaemia, hypertension and impaired glucose metabolism.

Aim of this study is to evaluate inflammation as an independent risk factor by using neutrophil to lymphocyte ratio (NLR).
Materials and methods
Patients who admitted to our outpatient clinic between January and December 2014 were assessed retrospectively. Patients diagnosed as diabetes, prediabetes, hypertension, thyroid dysfunction and any acute or chronic inflammatory disorder were excluded. A total of 437 female cases were included in the study. Cases were grouped according to BMI.
Results
Groups were age-matched ($P=0.513$). HOMA-IR and trigliseride values were positively, HDL levels were negatively correlated with BMI ($P<0.05$). There was no association between LDL values and BMI. There was no statistically significant difference between NLR values of groups 0, 1, 2 and 3. A trend toward higher NLR in group 4 was observed but the difference did not reach statistical significance ($P=0.117$). Group 5 however had significantly higher NLR values ($P=0.000$).

Group (BMI kg/m^2)	*n*	HOMA-IR	Trigliseride	HDL	LDL	NLR
0 (18.0–24.9)	45	1.33±0.63	90.67±47.71	58.79±15.43	123.48±50.51	1.85±0.68
1 (25.0–29.9)	86	1.93±0.89	106.42±62.13	53.30±14.85	133.31±39.83	1.86±0.53
2 (30.0–34.9)	98	2.43±1.29	126.00±59.38	46.93±11.89	135.40±33.55	1.75±0.63
3 (35.0–39.9)	76	2.80±1.50	147.10±75.07	48.48±15.20	131.03±36.28	1.79±0.56
4 (40.0–44.9)	67	3.87±2.26	152.17±70.21	46.64±21.46	130.19±32.46	2.28±0.53
5 (>45)	65	3.98±1.45	144.85±82.09	44.98±11.12	126.94±34.59	3.07±2.23

Conclusion
Increased NLR value is considered as an inflammatory marker and an indicator of cardiovascular risk. Our results established higher NLR values in morbid obesity patients and emphasised the increased cardiovascular risk in morbid obesity.

DOI: 10.1530/endoabs.37.EP582

EP583

A prospective prevalence study of functional adrenal insufficiency and its outcome in acute myocardial infarction in UKMMC

Norasyikin A Wahab, Shazatul Reza Mohd Redzuan, Norlela Sukor, Norlaila Mustafa, Oteh Maskom, Shamsul Azhar Shah & Nor Azmi Kamaruddin
Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia.

Introduction
Acute myocardial infarction (AMI) is a stressful condition in which it stimulates the hypothalamus-pituitary-adrenal axis leading to mark increase in the production of cortisol. Adrenal insufficiency (AI) has been shown to be associated with morbidity and mortality in acute coronary syndrome patients. To date, none study has been performed to determine prevalence of AI among patient with AMI.
Objectives
The aim of this study is to determine the prevalence of AI in AMI by using the low dose (LD) and standard dose (SD) synacthen tests and to correlate with morbidity and mortality.
Method
Fifty-six patients who fulfilled the diagnosis of AMI within 48 h of onset were subjected to LD (1 μg) synacthen test (LDST) followed by a SD (250 μg) synacthen test (SDST) 2-h later. Those who had AI, repeat synacthen test had to perform at day 30 of AMI.
Result
Thirty-five (62.5%) patients had ST elevation AMI and 21 (35.5%) non-ST elevation AMI. Using an increment of <250 nmol/l following LDST and SDST, 39 (69.6%) and 2 (3.6%) patients had adrenal insufficiency respectively. Based on LDST, the diagnosis of AI was associated with significant morbidity and mortality. One patient died during the study period and he had very high cortisol levels. Out of 15 patients who underwent repeat synacthen, only two of them had responded to the synacthen test.
Conclusion
Utilising the LDST, adrenal insufficiency was found in 69.6% of AMI patients. Mortality of AMI showed less cortisol increment to LDST but able to reach the peak cortisol level for both tests. Functional AI in AMI takes longer than 30 days to recover.
Disclosure
This study was approved by Research and Ethics committee of the Faculty of Medicine, UKM and the project code was FF-2014-214. Funding for this study was provided by the research Grant of Faculty Of Medicine UKM.

DOI: 10.1530/endoabs.37.EP583

EP584

Adipocytokine responses to acute exercise in athletes with different body fat content and sedentary controls

Marina Djelic[1], Sanja Mazic[1], Mirjana Sumarac Dumanovic[2], Tijana Durmic[1], Snezana Cvetkovic[3], Biljana Lazovic[4], Jelena Suzic Lazic[5] & Dragan Micic[2]
[1]Faculty of Medicine, Institute of Physiology, Belgrade, Serbia; [2]Faculty of Medicine, Institute of Endocrinology, Diabetes and Diseases of Metabolism, Belgrade, Serbia; [3]Faculty of Medicine, Clinical Centre Serbia, Belgrade, Serbia; [4]Faculty of Medicine, University Clinical Centre Zemun, Belgrade, Serbia; [5]Faculty of Medicine, University Clinical Centre Dragisa Misovic, Belgrade, Serbia.

The aim of this study was to investigate adipocytokine responses to an single bout acute exercise in elite athletes with a low percentage of body fat, elite athletes with a high percentage of body fat and sedentary controls. Sixteen athletes with low percentage of body fat (volleyball players, low fat athletes group, LFAG), 15 athletes with high percentage of body fat (the elite water polo players, high fat athletes group, HFAG) and 15 sedentary subjects participated in this study (age (years) 20±2; 20±2; 20±1, respectively). All subjects were exposed to anthropometric measurements and one bout exercise test on treadmill in order to examine acute changes of adipocytokines. Blood samples were obtained at baseline levels, immediately after the exercise test and 30 min after recovery. Separated serum or plasma were used for hormone (leptin, adiponectin and visfatin) ELISA analysis. In athletes in LFAG, baseline leptin concentration was significantly lower, but adiponectin and visfatin concentrations were significantly higher, compared to sedentary controls and athletes in HFAG ($P<0.05$, all). There were no significant post exercise or recovery changes in adiponectin concentration ($P>0.05$). No differences in leptin concentration over time were observed in athletes groups ($P>0.05$). In contrast, leptin concentration in sedentary controls was significantly reduced after exercise and decreased even more during the recovery period ($P<0.05$). Only in athletes in HFAG, visfatin concentration increased significantly after exercise, but reduces in recovery period ($P<0.05$). In controls, visfatin concentration was significantly reduced and stayed lower throughout the recovery period ($P<0.05$). In conclusion, our findings show leptin and visfatin levels, but not adiponectin respond to acute exercise. Acute exercise elicited an inverse visfatin response in athletes in HFAG and controls. Also, these results suggest that leptin is altered after acute exercise only in sedentary individuals.

DOI: 10.1530/endoabs.37.EP584

EP585

Anti-obesity effect of Aster spathulifolius Maxim extract

In-Jin Cho[1], Se Young Choung[2], Do Un Kim[3], You-Cheol Hwang[1], Kyu Jeung Ahn[1], Ho Yeon Chung[1] & In-Kyung Jeong[1]
[1]Department of Endocrinology and Metabolism, Kyung Hee University Hospital at Gangdong, Kyung Hee University School of Medicine, Seoul, Republic of Korea; [2]College of Pharmacy, Kyung Hee University, Seoul, Republic of Korea; [3]Newtree. Co., Ltd, Seoul, Republic of Korea.

Purpose
Aster spathulifolius Maxim is one of plants of chrysanthemum, which has shown an anti-obesity activity in diet induced mice model. We performed clinical trial for evaluating the anti-obesity efficacy and safety of Aster spathulifolius Maxim extract on obese human.
Methods
This study was randomised, double-blind, placebo-controlled clinical trial in Korea. A total of 41 obese subjects (BMI 25–30 kg/m^2) aged ≥20 years were randomized to one of two groups: i) placebo group ($n=20$), ii) Aster spathulifolius extract (AE) 700 mg/day ($n=21$). All subjects were instructed to take a pill of once-daily regimen for 12 weeks. Weight, BMI, waist circumference, fat mass (measured by bioimpedance method, DEXA, and abdominal computed tomography (CT)), and laboratory test were assessed at baseline and 12 weeks.
Results
Body weight was significantly decreased in AE group after 12-week treatment (placebo vs. AE: −0.08±2.11 kg vs −3.30±3.15 kg, $n<0.05$). Body fat mass reduction was significantly shown in AE group after 12-week treatment (placebo vs AE; bioimpedance method: −0.51±1.89 kg vs −2.38±2.30 kg, $P<0.05$; DEXA: 0.38±1.59 kg vs −2.26±2.37 kg, $P<0.05$; visceral fat area in CT: 8.11±18.13 vs −24.9±37.0 cm.sp, $P<0.05$; subcutaneous fat area in CT: 5.51±34.58 vs −24.4±31.8 cm.sp, $P<0.05$). Reduction of apo-B was significantly observed in AE group compared with placebo group (placebo vs

AE: 7.42±20.65 vs −2.76±15.86 mg/dl, $P<0.05$). The changes of fasting plasma glucose and HbA1c did not differ between two groups. In safety, there were no drug-related adverse events during the study.
Conclusion
In conclusion, Aster spathulifolius Maxim extract significantly decreases body weight, body fat, and apo-B level in obese human.
DOI: 10.1530/endoabs.37.EP585

EP586

The assessment of environmental and hereditary factors in obesity patients
Veranika Labashova, Alla Shepelkevich, Julia Dydyshko & Veranika Dovgalo
Belarusian State Medical University, Minsk, Belarus.

The aim of the research was to reveal and assess the interaction between environmental and hereditary factors in obese patients seeking for weight loss.
Materials and methods
We analysed the anamnesis of 134 overweight and obese patients, having asked to endocrinologist for losing weight (20 men and 112 women). The mean age of the respondents was 45.78+8, 76 years. 15.7% of patients were overweight, and 84.3% were obese. Heritability of obesity was determined according to family history of obesity, anamnesis of diabetes in relatives, childhood appearance of excess body weight. The environmental changes included eating habits, level of physical activity and water regime of participants.
Results
The assessment of the hereditary factors of obesity revealed that 76.5% (101 person) had a family history of obesity: 59.7% (80 patients) mentioned excess body weight on the maternal line and 40.3% (54 patients) described obesity for father's relatives. Diabetes was diagnosed in 14.9% (20 persons) – on the maternal line and in 9.7% (13 persons) on the fatherly line. 41% of respondents (55 patients) remarked childhood obesity in themselves. The analysis of environmental factors showed that 71, 7% of respondents skipping meals during the day, 13.4% (18 persons) had only one meal, 55.2% (74 persons) had 2–3 meals/day. Everyday moderate activity 30 min or more described only 11% of respondents, physical activity 30 min or less 3 days a week described 46% of patients, 30 min of activity 5–6 times a week 43% patients. The vast majority of patients 97.7% drank <2 l of water per day.
Conclusions
The occurrences of obesity relatives was 59.7% on the maternal line, 40.3% on the paternal line. Interaction with environment factors related to low physical activity and inadequate water consumption.
DOI: 10.1530/endoabs.37.EP586

EP587

Significance of cognitive-behavioural therapy in the treatment of obesity
Snjezana Popovic-Pejicic[1] & Zelija Velija-Asimi[2]
[1]University Hospitail, Clinical Center Banja Luka, Medical Faculty University of Banja Luka, Banja Luka, Republic of Srpska, Bosnia and Herzegovina; [2]Clinic for Endocrinology, Diabetes and Metbolic Disease, Sarajevo, Bosnia and Herzegovina.

Introduction
Dietary therapy (DT), programmed physical activity (PPA) and cognitive-behavioural therapy (CBT) are basic measures in the treatment of obesity. CBT applies methods which change eating habits of obese persons, aiming to remove barriers relating DT and PPA. The goal of this study is to try efficiency of applying CBT in the programme for the reduction of body mass of obese persons, vs the application of DT and PPA alone.
Design
The study included 60 obese persons, who were divided into two groups (1 and 2), with 30 patients in each group, 20–58 years of age, with the BMI ≥30 kg/m^2 and hyperlipidaemia (LDL-cholesterol ≥4.2 mmol/l serum). Patients have not been previously treated for obesity and were unhappy with their weight. Patients from both groups were on hypocaloric diet, individually designed and had programmed physical activity every day. Patient in group 2 underwent group CBT, under the supervision of psychiatrist once a week with duration of 120 min, but in group 1 no. Both groups also went to see an endocrinologist six times, on which occasions their body weight, parameters of lipid status serum and level of glucose in serum were measured. Results showed that in group 2, the medium value of BM reduction after 12 weeks of treatment was 9.5 kg (8.9%), LDL-cholesterol decreased for 34.5%, HDL-cholesterol increased for 2.7%, triglycerides decreased for 15.3%, glycaemia decreased for 14.8%, which is the significantly better metabolic profile, then in group 1.
Conclusion
CBT affected the improvement of motivation and readiness of patients to stick to the dietary regimen and physical activity. In designing the program for the reduction of obesity it is necessary to include CBT, which brings significantly better therapy outcomes, then the application of DT and PPA alone.
DOI: 10.1530/endoabs.37.EP587

EP588

Fine motor skill proficiency in obese children
David Gaul & Johann Issartel
Multisensory Motor Learning Lab, Dublin City University, Dublin, Ireland.

Introduction
Motor skill proficiency has shown to be a key predictor of children's engagement and enjoyment of regular physical activity. Recent evidence suggests that obese children have increased difficulties in the planning, initiation and control of motor skills compared to their normal weighted peers (D'Hondt *et al*. 2009, Gentier *et al*. 2013). These difficulties often manifest themselves as slower or less efficient performance of motor skills. This could impede the performance of everyday activities as well as affect their willingness to engage in physical activity. However the majority of research focuses on gross motor skill performance despite fine motor skills being prerequisites to many activities of daily living.
Methods
A sample of a 46 children were equally divided into two groups (obese (OB) vs normal weight (NW)) based on their BMI calculated using the IOTF cut points for children (Cole *et al*. 2000). Each group were equally matched for gender (11 male and 12 Female) and age ($M=9.101$ s.d. $=1.832$ and $M=9.103$ s.d. $=1.746$). The children were tested using the Fine Motor Skills Composite of the Bruininks Oseretsky Test of Motor Proficiency (BOT-2). The children's raw scores were converted according to the manual into standardised scores based on normative data.
Results
The OB group ($M=46.13$, s.d. $=9.16$) was found to score significantly lower ($P<0.05$) than their NW ($M=52.04$, s.d. $=5.36$) peers using the standard scores of the Fine Motor Skill Composite. This score represents whether a child possesses the expected level of fine motor skill for their age/gender.
Conclusion
The assumption that mass alone is responsible for these differences between BMI groups is not sufficient as additional body mass would only have a limited effect on fine motor skill. The above findings suggest the existence of a deficit in how OB children integrate and process sensory information compared to their normal weighted peers.
Disclosure
This work was supported by the Government of Ireland Postgraduate Scholarship Award 2014.
DOI: 10.1530/endoabs.37.EP588

EP589

High mean platelet volume in morbid obesity
Senay Arikan Durmaz[1], Zehra Bacanli[3], Ayse Carlioglu[2], Aydin Cifci[3] & Abdulmuttalip Arslan[2]
[1]Department of Endocrinology and Metabolism, Kirikkale University, Kirikkale, Turkey; [2]Department of Endocrinology and Metabolism, Erzurum Region Education and Research Hospital, Erzurum, Turkey; [3]Department of Internal Medicine, Kirikkale University, Kirikkale, Turkey.

Introduction and aim
The incidence of atherosclerotic vascular disease is high in obesity. Our aim is to determine the mean platelet volume (MPV) as a new indicator of atherosclerosis in morbid obesity.
Materials and methods
Thirty-three patients with morbid obesity who applied to endocrinology department (mean age 41.5±11.3 years, body weight 118.2±16.9 kg and BMI: 45.9±7.2 kg/m^2) and 39 age-matched (mean age 35.3±13.1 years; body weight 60.4±11.3 kg; BMI: 21.6±2.6 kg/m^2) healthy individuals were included in the study. Patients have haematological and other endocrinological diseases

were excluded from the study. All complete blood count analysis was performed by automatic analyser.
Results
We found that mean MPV values and platelet counts in morbid obesity group were higher than control subjects (8.7 ± 1.1 and 6.9 ± 0.5 fl, $P=0.0001$; 267 921.2 ± 81 475/mm^3 0.3; 163 710.8 ± 13 993.3 × 103/μl, $P=0.0001$, respectively). In addition, neutrophil lymphocyte ratio in morbid obesity group was not significantly different than those in control subjects (1.9 ± 0.7 and 1.7 ± 1.0, $P=0.225$, respectively). In addition, platelet to lymphocyte ratio was not statistically different between groups (102.9 ± 32.1 in morbid obesity and 104.8 ± 38.3 in control group). No statistically significant differences were found for the other parameters such as lymphocyte, WBC count and PCT. There were positive correlations both between MPV and BMI ($r=0.649$, $P=0.0001$) and between MPV and body weight ($r=0.599$, $P=0.0001$).
Conclusions
High MPV was associated with the presence of more metabolically active platelets. Therefore, increases of MPV in morbid obesity may lead to high risk for atherosclerosis.

DOI: 10.1530/endoabs.37.EP589

EP590

Genetic variation in GLP1 receptor is associated with interindividual differences in weight lowering potential of liraglutide in obese women with PCOS

Mojca Jensterle[1], Boštjan Pirš[2], Katja Goričar[2], Vita Dolžan[2] & Andrej Janež[1]
[1]Department of Endocrinology, Diabetes and Metabolic Diseases, University Medical Centre Ljubljana, Ljubljana, Slovenia; [2]Faculty of Medicine, Institute of Biochemistry, University of Ljubljana, Ljubljana, Slovenia.

Objective
The weight lowering potential of glucagon-like peptide (GLP) 1 receptor agonists (RAs) is interindividually different and clinically unpredictable. The potential role of genetic variability of GLP1R on body weight response to GLP1 RA has not yet been evaluated. The aim of the study was to assess the effect of common non-synonymous *GLP1R* single nucleotide polymorphisms (SNPs) rs6923761 and rs10305420 on weight loss in response to long acting GLP1 RA liraglutide in obese women with PCOS.
Methods
59 obese women with PCOS (aged 30.7 ± 6.9, BMI 38.4 ± 5.3 kg/m^2) were assigned to liraglutide 1.2 mg QD sc. for 12 weeks. They were genotyped for *GLP1R* rs6923761 and rs10305420. Changes of body mass, BMI, waist circumference and visceral adipose tissue (VAT) area were measured before and at the end of the study.
Results
After treatment intervention women lost on average 3.96 ± 3.24 kg ($P<0.001$), BMI was reduced for 1.44 ± 1.22 kg/m^2 ($P<0.001$), waist circumference for 3.31 ± 4.13 cm ($P<0.001$) and VAT for 7.05 ± 18.55 cm^2 ($P=0.002$). Twenty (34%) out of 59 subjects were good responders and lost 5% or more of their initial body weight. Carriers of at least one polymorphic rs10305420 allele had worse treatment response compared to carriers of two WT alleles (OR = 0.27, 95% CI = 0.09–0.85, $P=0.025$). Carriers of at least one polymorphic rs6923761 allele tended to have better treatment response compared to carriers of two WT alleles, but the difference was not statistically significant (OR = 3.06, 95% CI = 0.96–9.74, $P=0.058$).
Conclusion
Polymorphism of *GLP1R* rs10305420 accounts for interindividual differences in response to liraglutide regarding weight loss in obese women with PCOS. Future studies will determine whether such genetic variation may be clinically useful in prediction of the weight lowering potential of GLP1 RAs in obese individuals.

DOI: 10.1530/endoabs.37.EP590

EP591

The efficacy of lifestyle modification in preventing type 2 diabetes mellitus in subjects with impaired glucose homeostasis

Elena Shishko & Tatyana Mokhort
Medical, Minsk, Belarus.

Aims
The aim of our study is to assess the efficacy of lifestyle modification in preventing diabetes mellitus type 2 (DM 2)
Materials and methods
The study included 100 patients (69 m 258 f) 25–65 years with impaired glucose tolerance/impaired fasting glucose (IGT/IFG) and newly diagnosed DM 2. Patients were divided into two groups matched by sex, age, weight, BMI, waist-to-hip ratio (WHR). Research group included 54 patients who received and carried out recommendations of a balanced diet and physical activity. Control group included 46 patients who did not lifestyle modification. The study was 48 weeks. We measured fasting plasma glucose (FPG), 2-h plasma glucose concentrations (2-h PG) following a 75-g oral glucose tolerance test and related to fasting leptin (FL).
Results
Patients of the research group demonstrated reduction of BMI (-2.3 ± 3.1 kg/m^2) and WHR (-0.02 ± 0.025) ($P<0.01$ for all). They had positive dynamics of FPG and 2-h PG concentrations ($P<0.001$). Persons of the control group had increase BMI and WHR as also FPG and 2-h PG concentrations elevation ($P<0.05$). The main novel finding was that median serum leptin in research group decreased on −23.9% ($P<0.01$) and increased in control group on +27.6% ($P<0.01$). Among subjects with IGT from the research group, glucose levels normalised in 49.3% ($P<0.001$) and serum leptin levels decreased on 26.9% ($P<0.01$). In control group glucose levels normalized in 4.5% ($P<0.01$) persons with IGT. By the end of the study 12% of non-diabetic subjects with obese have developed DM 2 and 48% IGT. Among patients of the research group was a reduction of DM 2 by 11.9% and an increase in the control group by 35.1%.
Conclusion
Thereby, lifestyle modifications lead to reduction not only fasting plasma glucose, 2-h plasma glucose concentrations but and fasting leptin concentrations in individuals with impaired glucose tolerance.

DOI: 10.1530/endoabs.37.EP591

EP592

Relationship between thyroid hormone status and concomitant medication in hyperlipidaemic patients with statin induced adverse effects

Eszter Berta[1,2], Noémi Zsíros[3], Endre Nagy[1], György Paragh[3] & Miklós Bodor[1,2]
[1]Division of Endocrinology, Department of Medicine, University of Debrecen, Debrecen, Hungary; [2]Department of Clinical Pharmacology, University of Debrecen, Debrecen, Hungary; [3]Division of Metabolism, Department of Medicine, University of Debrecen, Debrecen, Hungary.

Statins are effective treatment for the prevention of cardiovascular diseases and used extensively worldwide. However, adverse effects induced by statins are the major barrier of maximalising cardiovascular risk reduction. Hypothyroidism and administration of drugs metabolised on the same cytochrome P450 (CYPP450) pathways where statin biotransformation occurs represent a significant risk factor for statin induced adverse effects including myopathy. Simvastatin, atorvastatin and lovastatin are metabolized by CYP3A4, fluvastatin by CYP2C9, while rosuvastatin by CYP2C9 and 2C19.
We investigated the levels of the free thyroid hormones and CYP metabolism of concomitant medication in 101 hyperlipidaemic patients (age 61.3 ± 9.9 years) with statin induced adverse effects including myopathy (56 cases; 55.4%), hepatopathy (39 cases; 38.6%) and gastrointestinal adverse effects (24 cases; 23.8%). Abnormal thyroid hormone levels were found in five patients (4.95%); clinical hypothyroidism in two and hyperthyroidism in three cases. 11patients had a positive history for hypothyroidism (10.9%). There were no significant differences in the TSH, fT_4 and fT_3 levels between patients with myopathy and patients with other adverse effects. 78 patients (77.2%) were administered drugs metabolized by CYP isoforms used by statins (3A4: 66 cases (65.3%); 2C9: 67 cases (66.3%); 2C19: 54 cases (53.5%)). Patients with myopathy took significantly more drugs metabolized by CYP3A4 compared to patients with other adverse effects ($P<0.05$). More myopathy cases were found in patients on simvastatin treatment (52% vs 38%, NS), while significantly less patients with myopathy were on fluvastatin treatment (13% vs 33%, $P<0.05$) compared to patients with other types of statin induced adverse effects. Both abnormal thyroid hormone status and administration of drugs metabolized by CYP3A4, 2C9 and 2C19 are common in our patients with statin induced adverse effects. Normalising the thyroid hormone status and optimising of the concomitant medication may reduce the risk of statin induced adverse effects.

DOI: 10.1530/endoabs.37.EP592

EP593

Is there a relationship between parathyroid hormone and obesity-linked disorders

Sule Temizkan, Sevin Demir, Kadriye Aydin, Hilal Toplu Ozturk, Aysenur Ozderya & Mehmet Sargin
Kartal Dr Lutfi Kirdar Training and Research Hospital, Istanbul, Turkey.

Introduction
Accumulating evidence indicate that high PTH resulting from primary or secondary hyperparathyroidism, is associated with hypertension, insulin resistance, dyslipidaemia, obesity, and cardiovascular mortality. Here, we aimed to show whether high PTH levels in obese population contribute the metabolic complications of obesity.
Methods/design
The medical records of all subjects attending the obesity outpatient clinic of Kartal Dr Lutfi Kirdar Training and Research Hospital in Istanbul between April 2014 and January 2015 were retrospectively evaluated. Subjects who had chronic illness, endocrine disease (diabetes mellitus, thyroid dysfunction, Cushing disease) and subjects with any medication were excluded. A total of 400 obese patients included in the study. Anthropometric, bioelectrical bioimpedence measures, blood examinations and 75-g glucose tolerance tests results were evaluated. Data are presented as means $\pm$ S.D.S for continuous or median (25 and 75% interquartiles) for non-normally distributed variables.
Results
Of the 400 obese subjects 335 were female. Mean age was 39 ± 10. Median BMI was 36 (34–41). Subjects were divided to quartiles according to blood PTH levels. Groups included Quartile 1 ($n=100$, median PTH; 42 (36–45)), Quartile 2 ($n=100$, median PTH; 55 (51–59)), Quartile 3 ($n=100$, median PTH; 73 (68–78)), Quartile 4 ($n=100$, median PTH; 99 (89–125)). Quartiles were evaluated with generalized linear model adjusted for age, sex and season of recruitment. Log was performed for non-normally distributed variables. Systolic and dystolic blood pressure, HOMA-IR, insulin sensitivity index (ISI), triglyceride (TG), HDL-cholesterol were not different among quartiles. Although, BMI was not different ($P=0.05$), trunk mean body fat (MBF) and percent trunk fat (PTF) were statistically different among quartiles ($P=0.03$, $P=0.01$, respectively).
Conclusion
Serum PTH adjusted for age, sex and season of recruitment, is positively associated with trunk MBF and PTF, but was not associated with obesity linked metabolic parameters.

DOI: 10.1530/endoabs.37.EP593

EP594

Cardiovascular disease in patients with primary hyperparathyroidism

Elena Brutskaya-Stempkovskaya[1], Alla Shepelkevich[1], Natalya Rekechinskaya[2], Tatyana Leonova[2] & Tatyana Churay[3]
[1]Belarusian State Medical University, Minsk, Belarus; [2]Minsk Cancer Center, Minsk, Belarus; [3]Minsk Endocrinology Center, Minsk, Belarus.

Introduction
Patients with primary hyperparathyroidism (PHPT) have an increased cardiovascular risk. However, the data on the relationship severity of PHPT clinical forms and prevalence of cardiovascular disorders are controversial.
Objective
Studying cardiovascular disease in patients with manifested forms of PHPT compared with mild forms.
Materials and methods
We studied 136 patients with PHPT (assesses arrhythmias, hypertension, coronary disease), a general medical examination were made. The indicators calcium and phosphorus metabolism (PTH, vitamin D, Ca general, Ca++, phosphates) were investigated.
Results
The mild PHPT were diagnosed in 54 patients with a mean age of patients was 51.5 ± 11.6 years, manifested forms PHPT were diagnosed in 82 patients, the average age of the patients was 52 ± 10.4 years. Cardiovascular disease were found in 19 (35.1%) patients with mild forms of PHPT and 38 (45.2%) with the manifested PHPT. A strong statistically significant correlation between the severity of clinical manifestations PHPT and incidence of cardiovascular disease in patients with PHPT ($R=0.81$, $P<0.05$).
Conclusion
These results suggest the high incidence of cardiovascular disease in patients with manifested PHPT and the low diagnostic rate of mild forms of PHPT.

DOI: 10.1530/endoabs.37.EP594

EP595

N-terminal pro-brain natriuretic peptide – an early independent predictor of anthracycline-induced cardiomyopathy

Alina Mihaela Pascu, Alina Bisoc & Mariana Radoi
Faculty of Medicine, Transilvania University of Brasov, Romania, Brasov, Romania.

Introduction
Early prediction of anticancer therapy cardiotoxicity is essential for applying proper preventive and supporting therapeutic strategies.
Objective
To evaluate plasma N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) related to cardiac dysfunction assessed by transthoracic 2D echocardiography (2D-TTE) in patients with cancer and early onset asymptomatic anthracycline-induced cardiomyopathy (AIC).
Methods
Prospective study of 68 patients with cancer treated with anthracyclines, followed up for 6 months. Diagnosis of AIC was set at 6 months by decreasing of left ventricular ejection fraction (LVEF) below 50% or with more than ten units or 20% from baseline. NT-proBNP and 2D-TTE were assessed at enrolment, and thereafter at 3 and 6 months.
Results
Fifteen (22.1%) patients developed AIC at 6 months of anthracycline treatment (group 1), and 53 (77.95%) patients did not evolve with AIC (group 2). At 3 months, in patients from group 1 NT pro-BNP was significantly higher compared to group 2 (121.0 (119.8; 140.8) pg/ml vs 97.7 (75.5; 111.7) pg/ml, $P=0.0001$, values expressed as median (25th; 75th percentiles)). Left ventricular (LV) diastolic dysfunction was significantly more frequent in group 1 (93.3%) vs group 2 (37.7%), $P=0.0002$. NT-proBNP at 3 months proved accurate in predicting asymptomatic AIC at 6 months (area under the receiver operating characteristic curve (AUC)$=0.845$, 95% CI: 0.735–0.954, $P=0.0001$). New-installed diastolic dysfunction at 3 months had a sensitivity of 60%, a specificity of 77% in predicting AIC at 6 months. NT-proBNP assessed at 3 months above a cut-off $=118.5$ pg/ml was an independent predictor of AIC at 6 months.
Conclusions
Plasma NT-proBNP at 3 months of anthracycline therapy proved to be an early independent predictor of asymptomatic anthracycline-induced cardiomyopathy.

DOI: 10.1530/endoabs.37.EP595

EP596

Increased expression of ATP-binding cassette transporter A1 by cilostazol may be a possible mechanism for its protective effect against hepatic steatosis

Bong-Soo Cha[1], Tae Sun Park[2], Byung Hun Jeon[1], Yong-Ho Lee[1], Mi Ra Yun[1], Byung Wan Lee[1], Eun Seok Kang[1] & Hyun Chul Lee[1]
[1]Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Chonbuk National University Medical School, Jeonju, Republic of Korea.

Objective
Cilostazol, a selective inhibitor of phosphodiesterase 3, which has been widely used in patients with atherosclerotic diseases, is known to have additional beneficial effects on dyslipidemia. ATP-binding cassette transporter A1 (ABCA1) plays a critical role in the regulation of intracellular cholesterol levels in hepatocytes. We aimed to investigate the effect of Cilostazol on hepatic steatosis and its underlying mechanism related to ABCA1.
Methods
Male C57BL/6 mice were randomly divided into three groups: i) fed normal chow diet with vehicle. ii) fed high-fat diet (HFD) with vehicle. iii) fed HFD with

Cilostazol. Cilostazol (30 mg/kg) was orally administered once daily for 9 weeks. Oral glucose tolerance test was done and liver tissues were examined. HepG2 cells were also used as an *in vitro* model by incubating with saturated fatty acid (palmitate) in the presence or absence of Cilostazol.
Results
In HFD-fed mice, Cilostazol treatment significantly decreased hepatic fat and liver weight. Cilostazol-treated mice also showed improved glucose tolerance and decreased levels of serum LDL, VLDL and total cholesterol. The expression of ABCA1 was significantly increased in the liver of cilostazol-treated mice by 2.4-folds ($P<0.05$) compared to HFD-fed control mice. In palmitate-treated HepG2 cells, lipid accumulation was significantly decreased after treatment with Cilostazol. Palmitate reduced the expression of ABCA1, which was restored with Cilostazol treatment by 1.3-folds ($P<0.05$). The HDL-cholesterol levels in the cell cultured media were also increased, while intracellular LDL and VLDL-cholesterol levels were decreased in HepG2 cells treated with palmitate and cilostazol compared to those with palmitate only.
Conclusion
Our results showed that cilostazol ameliorated hepatic steatosis by increasing ABCA1 expression in the hepatocytes. This implicates that cilostazol may have a beneficial role in the treatment of non-alcoholic fatty liver disease.

DOI: 10.1530/endoabs.37.EP596

EP597

Exploratory study a Brazilian population with multiple chronic conditions from the perspective of smoking

Arise Galil[1], Kimber Richter[2], Eliane Banhato[1], Tatiane Campos[1], Rafael Henrique Santos[1], Marilaine Souza[1], Mariane Almeida[1], Sonielle Oliveira[1], Fernando Colugnati[1], Ana Paula Cupertino[2] & Marcus Bastos[1]
[1]Federal University of Juiz de Fora, Juiz de Fora, Minas Gerais, Brazil; [2]Kansas University, Kansas City, Missouri, USA.

Recent evidence shows that are modifiable risk factors and preventable, the most responsible for the high morbidity and mortality secondary to multiple chronic conditions (MCC), and smoking is one of the most important representatives. However, we still lack studies of populations with MCC and its association with smoking status.
Objectives
To identify clinical and psychosocial characteristics according to the status of smoking among users with MCC, at high cardiovascular risk.
Methods
Cross-sectional study with evaluation of socio-demographic, clinical and laboratory data, in HIPERDIA Center Juiz de Fora, Minas Gerais (CHM-JF), Brazil, assisting users with MCC (hypertension, diabetes mellitus and chronic kidney disease). To check the status of smoking was considered smokers (S), former smokers (FS) and nonsmokers (NS). Control blood pressure (systolic blood pressure <130 mmHg); metabolic (normal fasting blood glucose <100 mg/dl and/ or regular glycated hemoglobin $<7\%$, for users <60 and $<8\%$ for those with ≥ 60 years); Normal LDL-cholesterol (<100 mg/dl); chronic kidney disease absent, the glomerular filtration rate (GFR) >60 ml/min per SC. Depression (PHQ-2 ≥ 3 points) and alcohol abuse (AUDIT-C >5 points). Declared atherosclerotic disease, DAD (vascular damage documented, regardless of the affected territory).
Results
1558 users reviews, of which 12% were S; 41% and 47%, FS and NS. Compared to FS and NS, S were younger, less obese and more often female, higher prevalence of low education, physical inactivity, depression, alcohol abuse and lack lipid. Additionally, FS had better lipid control in relation to S and NS. Chronic obstructive pulmonary disease (COPD) and DAD were more prevalent among S and FS, even after adjusting for confounding variables.
Conclusion
The current smoking was more common in the younger population, sedentary, alcohol abuse, depressive symptoms, users declared atherosclerotic disease, COPD and a history of cancer. These data gave to S, a worse clinical profile compared to the NS. For despite the termination, the FS remained with similar comorbidities that active smokers.

Disclosure
The project was approved by the Research Ethics Committee of the Federal University of Juiz de Fora, Opinion 283/2011 in 24/04/2012, funded by the National Institutes of Health Fogarty.

DOI: 10.1530/endoabs.37.EP597

EP598

TNFα induces lipolysis by downregulating CIDEC via MEK/ERK-dependent PPARγ phosphorylation and nuclear exportation

Xinrui Tan, Meizhen zhang & Yanfeng Xiao
The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.

CIDEC is a lipid droplet-targeting protein that promotes triglyceride accumulation and inhibits lipolysis. CIDEC is regulated by peroxisome proliferator-activated receptor γ (PPARγ). Previous studies demonstrate that CIDEC down-regulation is involved in TNFα-induced lipolysis. Here, we focus on the signalling pathway to clarify the mechanism of TNFα-mediated CIDEC down-regulation. CIDEC is significantly decreased in subcutaneous adipose tissue in obese subjects. Also, CIDEC mRNA expression inversely correlates with serum TNFα levels in our cohort of 68 patients. Using SW872 human adipocyte-differentiation model, we verify that TNFα causes lipolysis and CIDEC down-regulation in a dose and time-dependent manner.10 ng/ml TNFα almost abolishes CIDEC protein expression at 12-h exposure, while the MEK/ERK inhibitor U0126, but not the JNK inhibitor SP600125 or the P38 inhibitor SB203580, blocks this response. In addition, RNAi Knockdown of ERK1/2 inhibits TNFα-induced CIDEC down-regulation and phosphorylation of PPARγ. Furthermore, depletion of MEK1/2 which are the upstream activators of ERK1/2 reverse CIDEC down-regulation to a larger extent. Immunostaining of PPARγ and subcellular fractionation confirm that MEK1/2 rather than ERK1/2 mediate PPARγ nuclear exportation. Taken together, TNFα down-regulates CIDEC protein levels due to phosphorylation and nuclear export of PPARγ by MEK/ERK cascade and this adds new aspects of TNFα-induced lipolysis.
Disclosure
This work was supported by National Natural Science Foundation of China No. 81172689.

DOI: 10.1530/endoabs.37.EP598

EP599

Magnitude of overweight and obesity amongst school children in Delhi, India

Umesh Kapil
All India Institute Of Medical Sciences, New Delhi, India.

Obesity has emerged as an epidemic in India. The present study was conducted to assess the magnitude of overweight and obesity amongst children in the age group of 5–18 years belonging to low, middle and high income group in National Capital Territory NCT of Delhi. A total of 16 595 children (LIG 5087, MIG 5134 and HIG 6368) were covered in the present study. Overweight and obesity were assessed using BMI and triceps skin fold thickness (TSFT) utilizing age and sex specific cut off points. Considering the BMI cut off points, the prevalence of obesity and overweight in Low Income Group (LIG) school children was 0.1 and 2.7% respectively, amongst Middle Income Group (MIG) school children it was 0.6 and 6.5% and in High Income Group (HIG) school children was 6.8 and 15.3% respectively ($P<0001$). With regard to the TSFT criteria, the prevalence of obesity and overweight in LIG school children was 1.2 and 2.4%, amongst MIG school children it was 2.5 and 4.9% and in children belonging to HIG schools was 9.3 and 13.1% respectively ($P<0.001$). The present study documented that the prevalence of overweight and obesity was higher in the HIG children as compared to the MIG and the LIG for all age groups, highlighting the possible role of change in the dietary pattern and physical activities with increase in income levels.

DOI: 10.1530/endoabs.37.EP599

EP600

Altered sensory motor integration of obese adults

Johann Issartel[1], David Gaul[1], Arimin Mat[2] & Donal O'Shea[2]
[1]Multisensory Motor Learning Lab., Dublin City University, Dublin, Ireland; [2]Department of Endocrinology, St Vincent's University Hospital, Dublin, Ireland.

Introduction
It appears recently that the lack of physical activity might not be a factor for obesity but rather a consequence of perceptual-motor difficulties (D'Hondt *et al*. 2011). Perception and action are two intertwined processes: perception is a means to action and action is a means to perception. Not being able to perceive correctly visual or auditory information would alter someone's movement kinematics of any given task. The key question is how do these different senses interact in situations that rely on the tight coupling between perception and action? To which extend obesity modifies the sensory motor integration and the movement output?
Methods
88 participants (44 Obese and 44 matched-control) sat on a chair equipped with a wrist pendulum that moves in the sagittal plane. The pendulum had a potentiometer built-in that records the angular wrist movement. For one of the experimental conditions, an oscillating visual stimulus was displayed on the screen. Another experimental condition consisted of an auditory signal oscillating between the right and left ears of the participants. The task was to synchronise the pendulum with either or both sensory modalities.
Results
The key findings from the repeated-measures ANOVAs revealed a strong reduction of the movement accuracy of the obese participants. For all sensory modalities, patients struggled to synchronise their action with the stimuli ($P<0.05$). To make an analogy with a dance performance, one can imagine someone dancing off the beat of the music. The movement variability of the obese patients was also higher than the control group ($P<0.05$).
Conclusion
This perceptual problem reduces the motor control of obese patients revealing even more encompassed difficulties. The identification of the origin of the perceptual problem will allow us to address the problem to its source and eventually to break the vicious circle of a deficient perception and action coupling.

DOI: 10.1530/endoabs.37.EP600

EP601

The effectiveness of an integrated approach in the treatment of obesity

Irina Bourko[1], Maksim Lushchyk[1], Aleksey Romanousky[1], Olga Isachkina[2], Galina Korolenko[2], Elena Kholodova[1] & Larisa Danilova[1]
[1]BelMAPE, Minsk, Belarus; [2]10 City Hospital, Minsk, Belarus.

Introduction
To assess the effectiveness of treatment of obesity using complex integrated approach. In the treatment of obesity were used: instructions of patient in healthy eating habits, diet, taking medication that reduces fat absorption – lipid-adsorbent tablets, polyglucosamine (L112). Survey of patients was conducted. The received data were analysed.
Description of methods
61 obese patients (18 males and 43 females) were followed up for 12 weeks. Mean age 48.2 ± 9.2 years; BMI 34.9 ± 5.21 kg/m^2. BMI, waist circumference (WC) measurements, visceral fat content (%) before and after treatment were measured. Levels of total cholesterol (TC), triglycerides (TG), LDL cholesterol (LDLC), and HDL cholesterol (HDLC) were also measured.
Results
Followed up patients reached weight loss by 3.7%, in BMI of 1.31 kg/m^2, WC decreased by 4.15 cm, visceral fat by 0.68%. Metabolic parameters improved. The maximum effect was achieved among the patients with university education, stable job, motivation to lose weight and among those that were keeping a food diary.
Conclusion
An integrated approach in treatment of obesity is effective and consists of education of patients, presence of motivational reasons to lose weight, level of education, adherence to the principles of healthy eating and receiving supplementary medication to reduce fat absorption.

DOI: 10.1530/endoabs.37.EP601

EP602

SHBG-C57BL/ksJ-*db/db*: a new mouse model to study the link between SHBG regulation and obesity development

Cristina Sáez López, Cristina Hernández, Rafael Simó & David Martínez Selva
Vall d'Hebron Research Institute, Barcelona, Spain.

Low plasma SHBG levels in overweight individuals are a biomarker for the metabolic syndrome and are predictive of type 2 diabetes and risk of cardiovascular disease. There are no *in vivo* models to study SHBG expression and regulation during obesity development. The main reason for this is that the obesity-prone rodent models cannot be used to study this issue since rodents unlike humans do not express the *SHBG* gene in their livers. We have developed by crossing the human *SHBG* transgenic mice with the C57BL/ksJ-*db/db* mice, a unique mouse model that expresses the human SHBG and it develops obesity. We have also used a set of human liver biopsies. The results obtained with the SHBG-C57BL/ksJ-*db/db* mouse model have allowed us to determine that the SHBG overexpression in the C57BL/ksJ-*db/db* reduced the body weight gain but did not change the metabolic profile of these mice. Moreover, we elucidated the molecular mechanisms and transcription factors causing the SHBG down-regulation during obesity development, which involved changes in liver hepatocyte nuclear factor 4 alpha (HNF4α) and peroxisome proliferator-activated receptor gamma (PPARγ) mRNA and protein levels. Furthermore, these results were confirmed using human liver biopsies. Finally, obese mice had reduced plasma SHBG and total and free testosterone levels when compared to lean mice. We have created the first mouse model that resembles what occurs in human obese subjects in terms of SHBG expression and regulation as well as the reduction of total and free testosterone levels. Future research using this unique mouse model will determine the role of SHBG in the development and progression of obesity, type 2 diabetes or fatty liver disease.
Disclosure
This work was supported by two grants from the Instituto de Salud Carlos III: CP08/00058, PI09/144, PI12/01357 and CIBERDEM (CIBER de Diabetes y Enfermedades Metabólicas Asociadas) an initiative of Instituto de Salud Carlos III.

DOI: 10.1530/endoabs.37.EP602

EP603

Adiponectin deletion impairs insulin signalling in insulin-sensitive but not insulin-resistant 3T3-L1 adipocytes

Cheol-Young Park[1], Eugene Chang[2] & Sungrae Kim[3]
[1]Kangbuk Samsung Hospital, Sungkyunkwan University, Seoul, Republic of Korea; [2]Ewha Womans University, Seoul, Republic of Korea; [3]Bucheon St. Mary's Hospital, Bucheon, Republic of Korea.

Aims
Previous reports have demonstrated that the adipocyte-derived peptide adiponectin is closely associated with insulin resistance due to its insulin-sensitizing and anti-inflammatory properties in peripheral tissues; however the autocrine effects of adiponectin remain elusive. This study investigated regulatory effects of adiponectin on glucose transport and insulin signalling in insulin-sensitive or insulin-resistant 3T3-L1 adipocytes.
Methods
3T3-L1 fibroblasts were transfected with non-target or adiponectin (ADN) siRNA and differentiated. Chronic treatment with insulin (24 h, 100 nM) was employed to induce insulin resistance in differentiated adipocytes. Insulin-stimulated glucose transport was measured and protein and mRNA levels were assessed by western blot and RT-PCR.
Results
Prolonged incubation with insulin significantly reduced insulin-stimulated glucose uptake, suggesting the development of insulin resistance and adiponectin mRNA expression. In this insulin-resistant condition, adiponectin deletion did not alter insulin-stimulated glucose uptake. In insulin-sensitive adipocytes, adiponectin ablation reduced insulin-stimulated glucose uptake, expression of IRS-1 and GLUT4, and GLUT4 translocation to the membrane. Adiponectin knockdown did not affect the activation of AKT and p38MAPK (phosphorylation form/total form), but significantly decreased the activation of AMPK in insulin-responsive adipocytes.
Conclusion
Adiponectin deficiency suppresses insulin-induced glucose uptake, insulin signalling, and the AMPK pathway only in insulin-responsive 3T3-L1 adipocytes.

DOI: 10.1530/endoabs.37.EP603

EP604

Who is the Belarusian citizen seeking for losing weight?!

Veranika Labashova, Alla Shepelkevich, Julia Dydyshko & Veranika Dovgalo
Belarusian State Medical University, Minsk, Belarus.

Backgrounds and aim
Millions of people all over the world are in a search for the perfect weight loss plan. The aim of our research was to make a typical portrait of a Belarusian citizen who is trying to lose weight.
Methods
Participants were individuals ($n=70$) who were screened for a behavioral weight-loss treatment program. The majority of patients were women (88.4%). The mean age was 46.56+9.43 years. Among the participants three of 70 persons had normal BMI but felt themselves fat, 13 patients were overweight and 53 were obese (23 persons had BMI 30–34.9 kg/m^2; 14 persons – BMI 35.0–39.9 kg/m^2; and 17 persons BMI >40 kg/m^2). We analyzed the anamnesis of obesity, eating habits, physical activity, and comorbidity of the participants.
Results
We revealed that 18 of 67 participants (26.8%) had the excess weight from childhood, 17% of women become overweight after delivery. 41 of 67 persons (61.2%) had obese relatives on the maternal line, 28 of 67 persons (41.8%) on the paternal line. Among the participants 17 of 67 participants (25.3%) had hypertension and cardiovascular diseases, four of 67 (6%) registered hyperglycemia, 22.3% osteoarthritis. The majority of patients 52.2% made attempts to lose weight earlier; 47.7% of the participants follow unproven dieting advices; 19.4% used supplements and diet pills. The analyses of the eating habits revealed that 37.3% follow the starvation diet, 31.3% of participants were breakfast skippers. Physical activity <30 min five times per week was registered in 65.6% cases. The episodes of night eating described 8.9% participants. 13.4% of respondents felt teasing and social rejection.
Conclusion
Thus the typical obese Belarusian patient looking for losing weight is a women of 46.5 years old, who often had a severe anamnesis of obesity, series of comorbities, and disordered eating patterns.

DOI: 10.1530/endoabs.37.EP604

EP605

Long-term glucocorticoid concentrations as a risk factor for childhood obesity and adverse body fat distribution

Gerard Noppe[1,2], Erica L T van den Akker[2], Yolanda B de Rijke[3], Jan W Koper[1], Vincent W Jaddoe[4] & Elisabeth F C van Rossum[1]
[1]Department of Endocrinology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; [2]Department of Pediatrics, Sophia Erasmus MC, Children's Hospital, University Medical Center Rotterdam, Rotterdam, The Netherlands; [3]Department of Clinical Chemistry, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; [4]Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands.

Background
Childhood obesity is an increasing health problem, affecting over 40 million children aged 0–5 years worldwide. It is associated with premature onset of diabetes and cardiovascular disease in adulthood. Pathologically elevated cortisol is known to induce obesity and cardio-metabolic complications, suggesting cortisol is implicated in the onset of obesity. Indeed, recent pilot-studies showed an increase in hair cortisol concentrations in obese adults and adolescents. Additionally, polymorphisms in the glucocorticoid receptor (GR) gene increasing glucocorticoid (GC) sensitivity have been associated with metabolically adverse body composition.
Aim
To explore the role of GCs in the onset of obesity, we studied the associations of long-term GC exposure and genetically determined GC sensitivity with obesity and body fat distribution in children.
Methods
Average cortisol and cortisone concentrations over a 3-month period were measured by LC–MS/MS in scalp hair of 3019 6-year-old children participating in the Generation R study, a population-based cohort-study. Four polymorphisms (GR-9Beta, ER22-23EK, N363S, Bcl1) in the *GR* gene affecting GC sensitivity were genotyped. Anthropometrics were measured and DEXA scans were performed. World Obesity Federation criteria for weight-cutoffs were used.
Results
A total of 4.3% of the children were obese and 13.4% overweight. Long-term cortisol concentrations were associated with obesity (OR 10.3, $P<0.001$) and overweight (OR 1.5, $P<0.05$). Cortisone showed the same trend for obesity (OR 2.1, $P<0.05$), and overweight (OR 1.4, $P=0.08$). Cortisol and cortisone showed a positive linear association with BMI ($P<0.001$ and $P<0.01$), fat mass index (kg/height^2) ($P<0.01$ and $P<0.001$) and android/gynecoid fat mass ratio ($P=0.04$ and $P<0.001$). Fat mass index was increased in homozygous Bcl1− carriers ($P=0.03$). We found no effects of other polymorphisms.
Conclusion
Long-term GC levels are strongly associated with an increased risk of childhood obesity, and show linear associations with adverse fat distribution. The contribution of GR gene polymorphisms to body composition at the age of 6 years seems limited.
Disclosure
The Thrasher Research Fund, TRF11643.

DOI: 10.1530/endoabs.37.EP605

EP606

From genome to gene: genes and genetic variations to be associated with metabolic syndrome

Maryam Daneshpour[1], Bahareh Sedaghati Khayat[1], Mehdi Hedayati[1] & Fereidoun Azizi[2]
[1]Research Institute for Endocrine Sciences, Cellular and Molecular Endocrine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [2]Research Institute for Endocrine Sciences, Endocrine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Introduction
The prevalence of non-communicable disorders such as metabolic syndrome (MetS) is high in developing countries. MetS is a disorder of energy utilisation and storage, diagnosed by a co-occurrence of three out of five of the following medical conditions: abdominal (central) obesity, elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides, and low HDL cholesterol levels. The present review aims to discover the genetic variant reported in association with MetS.
Method and materials
The database for genotypes and phenotypes (dbGaP) and the database for genetic associations and human genome (HuGE navigator) were utilised in order to search for genes and their corresponding polymorphisms related to MetS. Additionally, an electronic literature search for other Iranian studies and the genetic aspect of TLGS was completed using PubMed.
Results
For phenotype selection in PheGenI, 30 traits were chosen and after the analysis, 21 of them were in common results with MetS. After finding the common variation between traits and MetS, omitting the repeated SNPs, 173 variations were remained. Finally, results distinguished six of the most important genetic regions found to have strong association with MetS.
Conclusion
Identifying major genes that are responsible for the MetS may improve the medical care for treating individuals with MetS, and eventually may lead to personalised medicine in which treatment is tailored genetically to the patient's needs. The present candidate regions is a respectable start to replicate genetic studies in large affected Iranian individual which we hope leads us to improve our medical care in this field.

DOI: 10.1530/endoabs.37.EP606

EP607

Audit of metabolic profiles in women with Turner syndrome

Ma Pyeh Kyithar & Siobhán McQuaid
Endocrinology Department, Mater Misericordiae University Hospital, Dublin, Ireland.

Introduction
Adults with Turner syndrome (TS) are at increased risk of cardiovascular morbidity and mortality. The aim of this study was to evaluate the compliance

with clinical guidelines (Bondy 2007) in measuring metabolic profiles in adults with TS.
Methods
Case notes of patients attending a dedicated TS clinic were studied. Variables assessed included anthropometric measurements, blood pressure (BP), fasting plasma glucose (FPG), HbA1c, fasting lipid profile, and thyroid function.
Results
Of 40 women with TS (mean age 35.9 years (18–56 years)), karyotyping was available on 70%: 17.5% had monosomy (45,X); 52.5% had other X chromosome abnormalities (mosaic 45,X/46,XX, ring X chromosome, isochromosome Xq, deletions Xp, and other structural abnormality of Y chromosome). Anthropometric and BP measurements were performed in all patients. FPG, HbA1c, fasting lipid profile, and thyroid function were measured in 90, 82, 92.5, and 100% of women respectively. 27.5% were overweight and 35% were obese. 10% had impaired glucose tolerance and 7.5% had type 2 diabetes mellitus. 67.5% had LDL-cholesterol between 2.5 and 4 mmol/l and 7.5% had LDL-cholesterol more than 4 mmol/l. 15% had triglycerides level between 1.7 and 2.3 mmol/l and 5% had triglycerides more than 2.3 mmol/l. 27.5% were on antihypertensive medications.17.5% were on cholesterol-lowering medications. 40% had primary hypothyroidism on L-thyroxine replacement. Systolic BP was significantly higher in monosomy group than those with other X chromosome abnormalities (128 ± 7 mmHg vs 117 ± 12 mmHg, $P = 0.034$). There were no significant differences in age, BMI, diastolic BP, HbA1c, lipid profiles, use of cholesterol-lowering medications or HRT between women with monosomy and those with other X chromosome abnormalities.
Conclusion
Service evaluation reveals good performance in measuring metabolic parameters in women with TS. Overweight/obesity, hypertension, and dyslipidaemia are common in our group of patients. Ongoing efforts are aimed at improving these cardiovascular risk factors.

DOI: 10.1530/endoabs.37.EP607

EP608

Metabolic syndrome and cardiovascular risk in frail elderly people

Olga Vasovic[1], Katarina Lalic[2,4], Danijela Trifunovic[3,4], Zvezdana Jemuovic[2] & Marina Nikolic Djurovic[2,4]
[1]Institute for Gerontology and Palliative Care, Belgrade, Serbia; [2]Clinic for Endocrinology, Diabetes and Metabolism, Clinical Center of Serbia, Belgrade, Serbia; [3]Clinic for Cardiology, Clinical Center of Serbia, Belgrade, Serbia; [4]Faculty of Medicine, University of Belgrade, Belgrade, Serbia.

Introduction
Objective of this study was to examine the importance of metabolic syndrome (MetS) as a predictor of cardiovascular mortality in frail elderly people.
Methods
Participants of the study were 253 community dwelling elderly aged 65–99 years. It was a prospective study with 32 months follow-up period. Patients were divided into four main groups according to the presence of MetS and prior major cardiovascular event (MACE): group A – patients without MetS and without MACE – the control group; group B – patients with MetS, without MACE; group C – patients without MetS, with MACE; and group D – patients with MetS and with MACE. We used Cox proportional hazards regression model for survival analysis. The results are presented as relative risk (RR) and 95% CI. Statistically significant differences were $P < 0.05$.
Results
The baseline mean age of participants was 82 years (78.3% women) (53.8% had prior MACE. During the study 109 patients (43.1%) died from cardiovascular cause of death. In our patients there was no statistically significant difference between four groups in functional ability, smoking habits and presence of hypertension. Women were more represented in groups with MetS compared with groups without MetS. Control group was statistically older than group D only. The best survival was in group B (75.9%), and the worst in group C (43.8%). Comparing to group B, participants in group C have almost three times higher risk for cardiovascular mortality (RR 2.978; 95% CI: 1.605–5.523; $P = 0.001$), whereas participants in group D have 2.5 times higher cardiovascular mortality risk (RR 2.457; 95% CI: 1.273–4.744; $P = 0.01$). Comparing to group A (the control group), only group C have statistically higher mortality rate (RR 1.894; 95% CI: 1.145–3.131; $P = 0.01$).
Conclusion
In our study, presence of prior MACE, but not the presence of MetS raises risk for cardiovascular mortality in frail elderly people.

DOI: 10.1530/endoabs.37.EP608

EP609

Investigation of the transient receptor potential channel gene expressions in metabolic syndrome

Suzan Tabur[1], Serdar Oztuzcu[1], Irfan Veysel Duzen[2], Ayten Eraydin[1], Mesut Ozkaya[1] & Abdullah Tuncay Demiryurek[1]
[1]Gaziantep University, Gaziantep, Sahinbey, Turkey; [2]25 Aralik State Hospital, Gaziantep, Sehitkamil, Turkey.

Introduction
Metabolic syndrome (MetS) is correlated with increased cardiovascular risk and characterized by several factors, including visceral obesity, hypertension, dyslipidemia, and insulin resistance. Several members of a large family of nonselective cation channels, e.g., transient receptor potential (TRP) channels, have been associated with the development of cardiovascular diseases. Thus, changes of TRP channel expression may account for the observed increased cardiovascular risk in MetS patients. The aim of this study was to investigate the possible contribution of TRP channel gene expressions in MetS.
Methods
A total of 54 patients with obesity-related MetS, and 41 healthy control subjects with similar age and sex were included to this study. mRNA from blood samples was extracted, and real-time PCR on the BioMark HD dynamic array system (Fluidigm, South San Francisco, CA, USA) was performed for the TRP channel gene expressions. For calculation of the significance of differences in gene expressions, the Mann–Whitney *U* test was used.
Results
We observed marked decreases in *TRPC1, TRPC3, TRPM2, TRPM5, TRPV4, TRPV5, TRPV6, MCOLN2* (*TRPML2*), and *MCOLN3* (*TRPML3*) gene expressions in MetS ($P < 0.05$). However, there was an augmentation in *TRPC6* gene expression ($P < 0.05$). No significant changes in expressions were found with *TRPA1, TRPC4, TRPC5, TRPC7, TRPM1, TRPM3, TRPM4, TRPM6, TRPM7, TRPM8, TRPV1, TRPV2, TRPV3, MCOLN1* (*TRPML1*), and *PKD2* (*TRPP2*) genes in MetS patients ($P > 0.05$).
Conclusion
This study revealed that there is a statistically significant relationship between TRP channels gene expressions and MetS. Our data showed that TRP channel gene expressions may contribute to the pathology of MetS.
Disclosure
This study was supported by a project (TF.13.20) from the University of Gaziantep.

DOI: 10.1530/endoabs.37.EP609

EP610

Linking temperature to metabolism: the role of brown adipose tissue in humans

Jenny Backhaus, Leonie Rademacher, Alexander Iwen, Maren Waltl, Melanie Noll, Hendrik Lehnert & Sebastian M Schmid
Department of Internal Medicine 1, Lübeck, Schleswig-Holstein, Germany.

The increasing prevalence of obesity is paralleled by related metabolic disorders such as insulin resistance and type 2 diabetes mellitus (T2DM). Extensive efforts across disciplines are made to reveal underlying mechanisms and develop effective therapies against obesity and its comorbidities. Since PET–CT studies provided evidence for functional brown adipose tissue (BAT) in adult humans, this specialized thermogenic compartment of adipocytes is in the focus of current research. Activated by moderate cold BAT utilises significant amounts of carbohydrates and fatty acids as substrates for heat production, thereby contributing to whole-body energy homeostasis. Beneficial metabolic effects of BAT activation lipid metabolism have been shown in mice and men. Here we assessed glucose homeostasis by Botnia clamping during cold-induced BAT activation in 15 healthy normal-weight men. Botnia clamp experiments combine an intravenous glucose tolerance test with a subsequent hyperinsulinaemic–euglycaemic clamp thereby allowing measurement of pancreatic β-cell capacity and peripheral insulin sensitivity within one session. BAT activation induced a highly significant 20% increase in glucose uptake due to improved insulin sensitivity while β-cell capacity remained unchanged as compared to thermoneutral conditions. Interestingly, resting energy expenditure and pituitary–thyroid axis activity as possible pathways linking BAT activation and glucose homeostasis were not affected during BAT activation. Although, underlying molecular mechanisms remain to be established in follow-up studies, these findings clearly highlight the metabolic significance of BAT activation in men and therefore might be a promising target for novel treatment approaches in obesity and T2DM.

Disclosure
This work was supported by the DFG, German Research Foundation (GRK 1957).
DOI: 10.1530/endoabs.37.EP610

EP611

C-reactive protein assay in obese paediatric patients: comparison of two laboratory methods

José Alves, Marta Manaças, Carolina Faria, Lia Filipe, Susana Silva & Helena Proença
Centro Hospitalar Lisboa Norte, Hospital de Santa Maria, Lisbon, Portugal.

Introduction
Obesity as a pro-inflammatory state is associated to increased levels of C-reactive protein (CRP). CPR is considered as a cardiovascular (CV) risk independent marker and is being researched as a predictive atherosclerosis biomarker in obese children. The American Heart Association (AHA) recommends a three classes approach when aiming at CV risk stratification (low <1.0 mg/l; moderate 1.0–3.0 mg/l; and high >3.0 mg/l). These classes were extrapolated to the paediatric aged patients.
Objective
Compare the performance of two different CPR assays, using blood samples from an obese paediatric population.
Methods
79 patients were enrolled (convenience sample) (ages 12–17). Serum CPR levels were simultaneously assayed using two distinct analytical methods: Classic wide rage CPR assay (wrCPR Siemens Latex enhanced immunoturbidimetry; ADVIA 2400; CMD = 0.03 mg/l normalization: CRM 470 IFCC), and high sensitivity PCR (CardioPhase hsCRP Siemens BNproSpec Siemens CMD = 0.175 mg/l). SPSS 20V Software was used for statistical analysis.
Results
The correlation coefficient ($R=0.9971$) ($P<0.001$) (Pearson's test) showed a very strong positive correlation between the two assays ($y=1.26x-0.34$). The Bland–Altman dispersion plot, pointed that the inter assay (absolute (AD) and percentual (PD)) differences were in 95% CI (except one outlier (>10 mg/l) (AD) and the six lowest pairs (PD)). PCR values of both assays were stratified according to AHA CV risk classes (72 pairs (91.14%) were grouped in the same class, including the aforementioned six lowest pairs). The Fleiss' test ($\kappa=0.858$) ($P<0.001$) showed a very strong AHA class agreement of both assays.
Conclusion
A strong correlation and agreement has been shown between the two assays.

DOI: 10.1530/endoabs.37.EP611

EP612

Does IGF influence the prognosis 10 months after myocardial infarction?

Yücel Yılmaz[1], Fatih Tanrıverdi[2] & Mustafa Altay[3]
[1]Department of Cardiology, Kayseri Education and Research Hospital, Kayseri, Turkey; [2]Faculty of Medicine, Erciyes University, Kayseri, Turkey; [3]Department of Endocrinology and Metabolism, Keçiören Education and Research Hospital, Ankara, Turkey.

Introduction
We investigated the levels of IGF1 in acute myocardial infarction (AMI) and sought to determine whether a decrease might influence the long-term prognosis.
Material and methods
Sixty-five patients who were admitted to our hospital with AMI were included in the study along with 26 other patients without coronary artery disease (CAD) who served as the control group. Fasting blood samples of all of the patients with AMI were obtained at the hospital and ~10 months later in order to evaluate their IGF1 and IGF-binding protein 3 (IGFBP3) levels.
Results
In the patients with AMI, the IGF1 levels were higher than in the control group ($P=0.002$). At the 10th month, the levels of IGFBP3 were significantly higher, and the IGF1 levels were higher but were not more significant than those in the control group ($P=0.006$ and $P=0.05$ respectively). When we compared the 10-month and baseline values, the levels of IGFBP3 were significantly higher at 10 months. In addition, the IGF1 levels were lower but did not achieve significance at 10 months ($P=0.04$) or at the time baseline measurements were taken ($P=0.06$). Furthermore, no significant differences were found between the patients with low or high IGF1 and IGFBP3 levels at the two different time periods when they were compared in terms of cardiac events.
Conclusion
At the 10-month follow-up after AMI, the serum total IGF1 and IGFBP3 levels were still high, and no correlations existed between the IGF1 and IGFBP3 levels and cardiac events.

DOI: 10.1530/endoabs.37.EP612

EP613

Association between the transient receptor potential channel gene polymorphisms and metabolic syndrome

Suzan Tabur[1], Serdar Oztuzcu[1], Irfan Veysel Duzen[2], Sercan Ergun[1] & Mesut Ozkaya[1]
[1]Gaziantep University, Gaziantep, Sahinbey, Turkey; [2]25 Aralik State Hospital, Gaziantep, Sehitkamil, Turkey.

Introduction
Metabolic syndrome (MetS) is characterised by a combination of visceral obesity, hypertension, insulin resistance, dyslipidemia, and impaired glucose tolerance. It is a prominent risk factor for cardiovascular morbidity and mortality. The etiology of MetS is complex. The progression of MetS is influenced by genetic susceptibility and environmental factors. The aim of this study was to investigate a possible association between transient receptor potential (TRP) channels gene polymorphisms and MetS in a Turkish population.
Methods
A total of 142 patients with obesity-related MetS and 166 healthy controls with similar age and sex were enrolled to this study. Genomic DNA from the participants was analyzed by a BioMark 96.96 dynamic array system (Fluidigm, South San Francisco, CA, USA). For calculation of the significance of differences in genotype and allele frequencies, the χ^2 test or Fisher's exact test was used. A P value of <0.002 (0.05/25) was considered statistically significant after Bonferroni's correction for multiple testing.
Results
There was an increase in A allele (64.6% in patients vs 49.5% in controls) and decrease in G allele frequencies (35.4% in patients vs 50.5% in control, $P=0.0019$) of the *TRPM5* gene rs4929982 (Arg578Gln) polymorphism. We also observed that the distribution of genotype and allele frequencies of the *TRPM8* gene rs12472151 in MetS patients were significantly different from controls ($P<0.0001$). However, no associations were found with the other 23 polymorphisms studied.
Conclusion
In conclusion, to the best of our knowledge, the present case–control study is the first to examine the potential involvement of TRP channel gene variations in the risk of incident MetS. Our data showed that genetic polymorphisms in *TRPM5* and *TRPM8* genes may modify individual susceptibility to MetS in the Turkish population.
Disclosure
This study was supported by a project (TF.13.20) from the University of Gaziantep.

DOI: 10.1530/endoabs.37.EP613

EP614

Effects of omega-3 fatty acid on pre- and post-prandial triglyceride and metabolic parameters with standard meals in patients with hypertriglyceridemia: open, multicentre study

Won Jun Kim[1], Sangmo Hong[2], Jun Goo Kang[3] & Chang Beom Lee[2]
[1]Department of Endocrinology and Metabolism, Gangneung Asan Hospital, University of Ulsan College of Medicine, Gangneung, Republic of Korea; [2]Department of Endocrinology and Metabolism, Hanyang Guri Hospital, University of Hanyang College of Medicine, Guri, Republic of Korea; [3]Department of Endocrinology and Metabolism, Hallym University Sacred Heart Hospital, Hallym University School of Medicine, Pyungchon, Republic of Korea.

Introduction
Nonfasting duration is much longer than fasting time in a day. Although there is a few reports on the importance of postprandial triacylglycerol (TG) on cardiovascular outcome, TG variation after meal is one of main obstacle of clinical trial. The purpose of this study is to determine effects of a 6-week period of omega-3 fatty acid supplementation on fasting and postprandial TG and metabolic parameters in response to standard test meals.
Methods
The study population included 26 patients with hypertriglyceridaemia ($\geq$200 mg/dl). They were educated and randomly allocated to treatment group by omega-3 fatty acid supplementation (Omacor, 2 g/day) or control group, and followed-up for 6 weeks in three hospitals. At days 1 and 42 visit, fasting and postprandial-3 h data were obtained respectively, before and after standard meals with 710 kcal.
Results
In intragroup analysis, treatment group with omega-3 fatty acids showed significant decrease on fasting TG (258.2 mg/dl vs 254.2 mg/dl, $P=0.046$) and especially post-prandial TG (357.3 mg/dl vs 277.2 mg/dl, $P=0.033$), while control group showed no significant difference during follow-up (271.2 mg/dl vs 255.1 mg/dl, $P=0.790$ for fasting TG and 343.7 mg/dl vs 324.7 mg/dl for post-prandial TG). However, in intergroup analysis, there was no significant difference between two groups in fasting and post-prandial TG (% change: $P=0.287$ and 0.303 respectively). There was no significant improvement in other lipid profiles. No significant adverse events were registered during this study.
Conclusion
The omega-3 fatty acids achieved a significant reduction of fasting and post-prandial triglycerides without adverse reactions. Because the trend of improvement in post-prandial TG appeared in the treatment group than control group, further study including more subjects will be needed.
Disclosure
This study was supported by Gun-il Pharmacy, Seoul, Korea.
DOI: 10.1530/endoabs.37.EP614

EP615

Neutrophil to lymphocyte ratio: relationship with anthropometric and metabolic parameters in morbidly obese patients

Cristina Serbanescu[1], Liliana Topor[1], Ivona Gheorghe-Fronea[1], Alexandra Nila[1], Anca Sirbu[1,2] & Simona Fica[1,2]
[1]Elias Emergency University Hospital, Bucharest, Romania; [2]University of Medicine and Pharmacy 'Carol Davila', Bucharest, Romania.

Introduction
Obesity is generally associated with a chronic state of subclinical inflammation. The assessment of the inflammatory status is routinely made by measuring circulating levels of nonspecific proinflammatory markers. Neutrophil to lymphocyte ratio (NRL) is a new simple inflammatory marker which can be reliable in evaluating the inflammatory status occurring in morbidly obese patients. The aim of this study was to investigate the relationship between NLR as an index of chronic inflammation and anthropometric and metabolic parameters in a group of morbidly obese patients.
Patients and methods
Our study included 415 patients (130 men) with severe obesity (mean BMI$=45.46\pm8.68$ kg/m^2, mean age$=41.31\pm11.33$ years), who were evaluated clinically (medical history, anthropometrics, and blood pressure measurements) and biologically (blood count, complete metabolic tests, and leptin level) in a research program for bariatric surgery.
Results
NLR was significantly higher in women (2.33 ± 0.95 vs 2.09 ± 0.87, $P<0.05$) and in non-smokers (2.35 ± 1.01 vs 2.14 ± 0.81, $P<0.05$). After adjusting for gender and smoking status, NLR positively correlated with BMI ($r=0.132$, $P<0.01$) waist circumference ($r=0.225$, $P<0.001$), and waist/height ratio ($r=0.203$, $P<0.001$), as well as with systolic blood pressure ($r=0.136$, $P<0.05$), serum C-reactive protein ($r=0.170$, $P<0.001$), HOMA-IR ($r=0.121$, $P<0.05$), and serum leptin level ($r=0.172$, $P<0.01$). In a linear regression analysis, with NLR as dependent variable and factors previously shown to significantly correlate to its level as independent variables, gender, BMI, and systolic blood pressure remained independently associated with NLR.
Conclusions
Gender, systolic blood pressure, and adiposity level are independent determinants of NLR in severely obese patients. Further studies are needed to elucidate the association of this parameter with obesity complications and prognosis.
DOI: 10.1530/endoabs.37.EP615

EP616

A low glycaemic index, low glycaemic load snack based on stevia and fortified with vitamin D, improves metabolic/hormonal profile, and compliance in normal subjects and prediabetics; results from a 4 months, controlled trial

Sarantis Livadas, Antonia Dastamani, Charikleia Stefanaki, Emily Mantzou, Areti Painesi, Eleni Papanikolaou & George Chrousos
Endocrine Unit, Evgenidion Hospital, University of Athens Medical School, Athens, Greece.

Introduction
Half of subjects following a low-calorie dietary program cannot tolerate its nutritional restrictions and abandon it. A realistic approach to overcome this obstacle is the addition of low glycaemic index (GI), low glycaemic load (GL) snacks in their nutrition. Stevia, a potent, low calorie natural sweetener exerts anti-hyperglycaemic and insulinotropic activities. Furthermore, Vitamin D deficiency may affect diabetes development in the long run.
Aim
To assess a new bioactive, low GI/ low GL product, based on stevia glycosides and fortified with vitamins A and D, regarding metabolic/hormonal profile and the compliance of subjects undergoing a hypocaloric nutritional approach.
Methods
A 4-month controlled, prospective trial in healthy subjects ($n=80$) and prediabetics ($n=39$). 119 overweight/obese subjects were enrolled and given the same hypocaloric nutritional approach and the choice of either a stevia snack consumption (4/week, $n=60$) or the consumption of a personal choice dessert (1/week, $n=59$).
Results
In all groups, a significant weight loss was observed ($P<0.05$). In healthy subjects waist circumference, insulin, and HOMA index were significantly improved, irrespectively of the method of intervention ($P<0.05$). In prediabetics, insulin, HbA1c, HOMA index, CRP, and vitamin D levels were ameliorated only in the stevia group. The attrition rate was similar between groups ($\sim$8%), but the majority of the stevia group suggested that they preferred this approach.
Conclusions
The consumption of low GI, low GL snacks based on stevia and fortified with vitamin D, increases compliance in subjects following a nutritional programme and exerts a beneficial role on the metabolic/hormonal profile of people with prediabetes.
Disclosure
This work was supported by the Greek and Chinese General Secretariat for Research and Technology (grant number: 12CHN156).
DOI: 10.1530/endoabs.37.EP616

EP617

Intima–media thickness measurement of the carotid artery in patients with primary hyperparathyroidism

Dilek Tuzun, Ayten Oguz[1], Murat Sahin[1], Safa Ersen Ganidagli[2], Didem Atay[2], Hanife Bolat[2], Cansu Yilmaz Cabioglu[2], Ahmet Celik[3] & Kamile Gul[1]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey; [2]Department of Internal Medicine, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey; [3]Department of Biochemistry, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey.

Aim
The intima–media thickness (IMT) measurement of the common carotid artery is recognised as an important marker of systemic atherosclerosis. It may be useful in

predicting the cardiovascular events, since it is related to the severity of coronary artery disease. The aims of this study were to analyse whether correlations exist between the IMT of the common carotid artery and the main clinical and biochemical parameters in patients with primary hyperparathyroidism (PHPT).
Patients and methods
Thirty patients with biochemically confirmed PHPT (group A, cases), 26 patients (group B, control group who have DM and/or HT), and 24 healthy volunteers (group C, healthy controls) were prospectively enrolled in the study. All patients underwent ultrasound examination and the IMT of each carotid artery were recorded.
Results
The final pathology showed a solitary parathyroid adenoma in all cases. Age, sex, mean IMT, and biochemical parameters, except serum calcium and PTH, did not differ significantly between groups (Table 1). But IMT is higher than case group compared to the other groups. But it was not statistically significant ($P=0.05$). In group A, DM and/or HT rate was 37.5% while 32.5% in group B and 0% in group C. There was positive significant correlation between serum calcium and IMT ($r=324$, $P=0.003$). But there was no correlation between IMT and serum parathyroid hormone and or serum phosphate.

Table 1 Main clinical and biochemical parameters of groups.

	Group A	Group B	Group C	*P*
Age (years)	49.07±12.95	53.85±5.98	47.75±6.08	0.05
Sex (female/male) (*n*)	24/6	24/2	20/4	0.421
Ca (mg/dl)	11.45±1.04	8.88±0.44	9.02±0.43	<0.001
P (mg/dl)	2.76±0.48	2.96±0.16	2.94±0.13	0.05
PTH (pg/ml)	229.98±182.84	41.38±3.62	42.87±2.67	<0.001
IMT (mm)	0.83±0.14	0.76±0.19	0.72±0.51	0.05

Group A, cases; group B, controls with DM and/or HT; group C, healthy controls; PTH, parathyroid hormone; IMT, intima–media thickness of the common carotid artery.

Conclusion
Several cardiovascular risk factors have been reported in patients with PHPT since both calcium and PTH are related to heart function. Our results suggest that hypercalcaemia may represent a risk of carotid atherosclerosis in patients with PHPT.

DOI: 10.1530/endoabs.37.EP617

EP618

Impact of laparoscopic gastric bypass and sleeve gastrectomy on anti-hyperglycaemic medication use in pre-existing type 2 diabetes mellitus

Seamus O'Boyle, Hayder Shabana, Colm O'Boyle & Eoin O'Sullivan
Bon Secours Hospital, Cork, Ireland.

The beneficial effects of metabolic surgery on clinical and biochemical parameters in patients with type 2 diabetes are well-described. Laparoscopic sleeve gastrectomy has more recently gained recognition as an effective form of surgery along with laparoscopic gastric bypass. We wished to evaluate the impact on anti-hyperglycaemic medication use and glycaemic control in patients with pre-existing diabetes undergoing surgery by a single surgeon in the country's highest volume metabolic surgery unit. Between 2008 and 2013, 74 (28%) of 264 (176 gastric bypass and 88 sleeve gastrectomy) patients who underwent surgery had pre-existing diabetes. Mean duration of diabetes was 36 (1–240) months. Forty-six (62%) were female with median age 51 (33–75) years. Pre-operatively, 14 were diet controlled, 50 were on oral hypoglycaemic agents and a further ten were treated with insulin. Mean BMI and HbA1c pre-operatively were 48.6 (±7.0) kg/m^2 and 62.9 (±18.2) mmol/mol respectively. At a 12-month minimum post-operative follow-up, BMI had fallen to 34.0±6.3 kg/m^2 ($P<0.001$) and HbA1c to 45.3±11.7 mmol/mol ($P<0.001$). Of the 50 patients taking oral medications pre-operatively, 40 were able to discontinue all medications, and of the ten on insulin pre-operatively, seven no longer needed insulin therapy.
Our findings from the largest surgical Irish centre are in keeping with similar published international data and again demonstrate the positive benefit which may be seen in patients with diabetes undergoing metabolic surgery.

DOI: 10.1530/endoabs.37.EP618

EP619

Steroid hormones related to 11β-hydroxysteroid dehydrogenase in obese adolescents and non-obese controls

Ludmila Macova, Hana Zamrazilova, Barbora Sedlackova & Martin Hill
Institute of Endocrinology, Prague, Czech Republic.

Introduction
Elevated activity and expression of 11beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) are associated with the development of obesity and metabolic syndrome. This enzyme is responsible for majority of the extra-adrenal production of glucocorticoids. It regenerates active cortisol from biologically inactive cortisone. Human 11β-HSD1 also reversibly catalyzes the interconversion of 7α-hydroxy- and 7β-hydroxy-DHEA into 7-oxo-DHEA. In order to examine the role of 11β-HSD1 in human obesity, we followed the circulating levels of steroids related to 11β-HSD1 in obese patients and non-obese controls.
Methods/design
The cohort of 282 obese adolescents, 154 girls (median age 15.31, range 14.17–16.68 years) and 128 boys (median age 14.95, range 13.87–16.16 years), BMI >90th percentile and the cohort of 100 normostenic controls including 50 girls (median age 15.29, range 14.32–16.79 years) and 50 boys (median age 15.29, range 14.47–16.77 years), BMI 25th–75th percentiles were examined. Circulating levels of cortisol, cortisone, DHEA, 7-oxo-, 7α-hydroxy-, 7β-hydroxy-, and 16α-hydroxy-DHEA were analysed by liquid chromatography-tandem mass spectrometry method.
Results
We found significantly increased levels of cortisone in obese subjects, while cortisol levels did not differ between obese and normostenic adolescents. Higher circulating levels of DHEA in obese girls, higher 7β-hydroxy-DHEA in both sexes, higher 7-oxo-DHEA in obese boys and reduced levels of 16α-hydroxy-DHEA in obese girls were observed. While the absolute levels of circulating 7α-hydroxy-DHEA did not differ between examined groups, the 7α-hydroxy-DHEA/DHEA ratio was significantly lower in obese subjects suggesting reduced 7α-hydroxylation in obesity.
Conclusion
Our findings support a role of 11β-HSD1 as well as derivatives of DHEA in the control of human metabolism.
Disclosure
This work was supported by IGA MZCR NT/13542-3 and MH CZ – DRO (Institute of Endocrinology – EU, 00023761).

DOI: 10.1530/endoabs.37.EP619

EP620

Liraglutide improves surfactant protein-B production and reduces right ventricular hypertrophy in a rat model of intersitial pulmonary fibrosis

Juan Fandiño Gómez[1,2], Marina Romaní Pérez[3], Verónica Outeiriño Iglesias[1,2], Yolanda Diz Chaves[1,2], María González Núñez[1,2], Houcine Dab[4], Eva MaríaVigo Gago[1,2], Lucas González Matías[1,2] & Federico Mallo Ferrer[1,2]
[1]Faculty of Biology, University of Vigo, Vigo, Pontevedra, Spain; [2]Group of Endocrinology and Neurophysiology, Biomedical Research Center (CINBIO), University of Vigo, Vigo, Pontevedra, Spain; [3]Nutrineuro, University of Bordeaux, INRA, Bordeaux, Aquitaine, France; [4]Higher Institute of Applied Biology Medenine (ISBAM), University of Gabes, Medenine, Tunisia.

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and fatal lung disease characterized by excessive matrix deposition that disrupts the normal alveolar architecture and lung physiology. Glucagon-like peptide 1 (GLP1) is a gut-produced hormone with insulinotropic effects. GLP1 receptor is expressed in the lung where it is implicated in the synthesis of the protein (SPs) and lipid fractions of the surfactant. We have previously shown that the GLP1 receptor agonist, liraglutide (LIR), is able to restore surfactant protein-B (SP-B, a limiting factor for survival) production and right ventricular hypertrophy in streptozotocin-diabetic rats. The aim of this work was to study the effects of the GLP-1 receptor agonist liraglutide in the production of SPs, fibrosis indicators and right ventricle mass in a rat model of IPF. IPF was induced in rats by the single intratracheal instillation of bleomycin (BLM, 2.5 mg/kg). From day 10 rats were treated with liraglutide (100 μg/kg per 12 h s.c.), once overwhelmed the acute inflammatory phase, and then they were sacrificed in day 21. Heart ventricles and lungs were isolated, weighted, and frozen. The expression levels of SP-B, thyroid

transcription factor 1 (TTF1, a transcription factor for SP-B) and receptors for GLP1 and leptin were lower in lungs of BLM-treated rats; but their levels were restored by liraglutide treatment. The right ventricle weight was also augmented in BLM-treated rats and liraglutide administration partially restored right ventricle masses. We have also measured the expression levels of lung fibrosis indicators as collagen type-IαI and connective tissue growth factor (CTGF), which yielded higher levels in BLM-treated animals, but liraglutide did not modified those. In conclusion, we found that liraglutide was able to increasing pulmonary SP-B and partially reverse right ventricular hypertrophy associated to the lung fibrosis induced by BLM, however, it can't improve the interstitial fibrosis once consolidated.

DOI: 10.1530/endoabs.37.EP620

EP621

Metabolic syndrome and muscle mass

Nilay Ergen, Aslı Dogruk Unal, Ozlem Cigerli, Hulya Parildar, Ozlem Tarcin, Betul Ugur Altun & Nilgun Guvener Demirag
Baskent University Istanbul Hospital, Istanbul, Turkey.

Objective
Low skeletal muscle mass is an emerging risk factor for metabolic disorders. In this study, we aimed to evaluate the relationships between fat mass, muscle mass, muscle fat mass ratio, total fat mass, and abdominal fat mass ratio by comparing the body compositions in obese women with and without metabolic syndrome.
Methods
Totally 89 obese women (mean ± S.D., age 42.1 ± 12 years, BMI 36.5 ± 4.2%) with newly diagnosed metabolic syndrome (MS, $n=64$, case group) and without metabolic syndrome (NMS, $n=25$, control group) were included into study. Body composition was measured by bioelectrical impedance analysis (BIA). Metabolic syndrome was defined using the International Diabetes Federation 2005 diagnostic criteria.
Results
It was found that subjects with MS had 57.2 ± 13.2 kg muscle mass, 41.2 ± 8.9 kg of fat mass. Their muscle/fat ratio was 1.46 ± 0.49 and total fat/abdominal fat ratio was 1.99 ± 0.25. Subjects without MS had 53.5 ± 8.4 kg of muscle mass 39.2 ± 9.3 kg of fat mass. Their muscle/fat ratio was 1.44 ± 0.42 and total fat/abdominal fat ratio was 1.96 ± 0.37 and there was no statistical significant difference ($P>0.05$). On the other hand subjects who had MS and non-MS, fasting serum insulin and HOMA-IR values were 21.1 ± 11.8 and 11.3 ± 5.5 μU/ml; 5.5 ± 3.5 and 2.7 ± 1.5 μU/ml respectively ($P<0.01$).
Conclusion
There is evidence that reduction in muscle mass and muscle/fat ratio is a risk factor for metabolic syndrome, but we did not find any significant reduction of muscle mass in subjects with MS in this study. This study should be redesigned in larger population to evaluate the meaning of these results. This may be explained by the anabolic effect of increased serum insulin levels in metabolic syndrome patients.

DOI: 10.1530/endoabs.37.EP621

EP622

Increased FNDC5 (irisin) expression in subcutaneous adipose tissue in obese patients with type 2 diabetes 1 year after bariatric surgery

Julia Muenzker[1], Alexandra Harger[1], Alexandru Tuca[1], Lisa Lindheim[1], Verena Zachhuber[1], Eva Svehlikova[1], Oana Freisinger[2], Johanna Fruhmann[2], Friedrich Tadler[3], Thomas R Pieber[1] & Barbara Obermayer-Pietsch[1]
[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Medical University of Graz, Graz, Austria; [2]Department of Surgery, Medical University of Graz, Graz, Austria; [3]Department of Surgery, Krankenhaus der Elisabethinen, Graz, Austria.

Aim
Gastric bypass surgery improves glycaemic control, but the underlying mechanisms including potential changes in adipoinsular axis are incompletely understood. The aim of this study was to investigate potentially causal or associated alterations in gene expression of adipokines, myokines, and hormones in the subcutaneous and visceral adipose tissue of diabetic and non-diabetic obese subjects before and after gastric bypass.
Material and methods
Biopsy specimens from the subcutaneous adipose tissue of 12 diabetic and 12 non-diabetic patients at and 1 year after gastric bypass were analysed with quantitative real-time PCR for the expression levels of various adipokines, myokines, and hormones such as adiponectin, leptin, irisin (FNDC5), osteocalcin, and osteopontin.
Results
Non-diabetic subjects were found to express significantly higher levels of FNDC5 in the subcutaneous adipose tissue than diabetic subjects before gastric bypass ($P=0.0167$). FNDC5 expression in the subcutaneous adipose tissue of diabetic patients was significantly increased one year after surgery ($P<0.001$). In non-diabetic subjects, there was no significant increase observable ($P=0.158$). The increase in FNDC5 in diabetic subjects correlated with reduction in BMI (Pearson's $r=0.718$, $P=0.009$). No correlation was observed between FNDC5 expression and early insulin response or insulin sensitivity index.
Conclusion
To our knowledge, this is the first study to investigate the role of the novel myokine irisin in bariatric surgery mediated weight loss. The results of this study demonstrate that exercise-independent weight loss increases irisin expression levels in subcutaneous adipose tissue of diabetic subjects.

DOI: 10.1530/endoabs.37.EP622

EP623

Relationship between TSH and cortisol levels in euthyroid obese subjects

Neslihan Soysal-Atile[1], Betül Ekiz-Bilir[1], Bülent Bilir[2] & Sonat Dilek Kara[2]
[1]Endocrinology Department, Tekirdag State Hospital, Tekirdag, Turkey; [2]Internal Medicine Department, Namik Kemal University Faculty of Medicine, Tekirdag, Turkey.

Several studies have reported that TSH is positively correlated with obesity, dyslipidaemia, and impaired glucose metabolism even in normal range limits. We aimed to evaluate the TSH levels in a cohort of otherwise healthy obese women without clinical evidence of thyroid dysfunction.
Materials and methods
127 female patients were enrolled in this study. Anthropometric and laboratory measurements were retrospectively analysed. Patients were divided into subgroups according to BMIs.
Results
Groups were age-matched. No statistically significant correlation was found between TSH and BMI, HOMA-IR, triglyseride, HDL, or LDL values. But a significant positive correlation between TSH and cortisol levels was revealed ($P=0.000$). As expected, HOMA-IR and triglyseride values were positively, HDL levels were negatively correlated with BMI ($P<0.05$).
Conclusion
In our euthyroid cohort, we did not found any significant association between plasma TSH levels and obesity. However, the positive relationship between TSH and cortisol is a compelling finding. It's known that overt hypothyroidism is associated with frankly elevated cortisol levels. But our study finding suggested a correlation within normal range limits and requires further investigations in order to better understand the mechanisms involved in the TSH–cortisol relationship.

DOI: 10.1530/endoabs.37.EP623

EP624

Levels of advanced glycation end products (AGEs), AGE's receptor (sRAGE) and their relationship with cardiovascular risk factors in newly diagnosed type 2 diabetic patients

Etzabel Villegas-Rodriguez[1], Sergio Solorio-Meza[2], Martha Eugenia Fajardo-Araujo[1], Jaime Uribarri[3], Juan Manuel Malacara[1], Sofia Torres-Graciano[1] & Ma Eugenia Garay-Sevilla[1]
[1]Department of Medical Science, University of Guanajuato, Leon, Gto., Mexico; [2]Instituto Mexicano del Seguro Social, Leon, Gto., Mexico; [3]Department of Medicine, The Mount Sinai Health System, Incahn School of Medicine, Mount Sinai, New York, USA.

Diabetes is associated with a greatly increased risk of cardiovascular disease and the advanced glycation end products (AGEs) and their receptors play an important role in these complications.
Objective
To study the association between AGEs and sRAGE levels with cardiovascular risk factors in obese and non-obese newly diagnosed type 2 diabetic patients.
Material and methods
We conducted a cross-sectional study in subjects with type 2 diabetes mellitus of recent diagnosis, by means of a glucose tolerance test according to the ADA criteria (age 35–65). We studied two groups, one with obesity ($n=40$) and other with normal weight ($n=40$). We measured somatometric variables, SBP, DBP, glucose, HbA1c, lipid profile, insulin, HOMA-IR, serum AGEs, ICAM-1, VCAM-1, 8-oxo-DG, MDA, and sRAGE. We also measured carotid intima–media thickness (cIMT) and flow-mediated dilation (FMD) by ultrasound.
Results
We studied 80 patients with average age: 48 ± 7.3 years old and HbA1c: 6.53 ± 1.08. Serum AGEs ($P<0.0001$), sRAGE ($P<0.0001$), ICAM-1 ($P<0.0001$), VCAM-1 ($P<0.0001$), 8-oxo-dG ($P<0.0001$), MDA ($P<0.00$), HOMA-IR ($P<0.001$), and cIMT ($P<0.001$), were lower in the non-obese than in obese patients, while FMD ($P<0.02$) was higher in the obesity group. In the total group serum AGEs was associated with age ($P<0.02$), ICAM-1 ($P<0.0001$), and HOMA-IR ($P<0.01$); in the obesity group, sAGEs were associated with age ($P<0.01$), HbA1c ($P<0.01$), HOMA-IR ($P<0.0001$), and in the normal weight subjects with FMD ($P<0.001$). In the total group sRAGE were associated with VCAM-1 ($P<0.0001$), ICAM-1 ($P<0.001$), MDA ($P<0.001$), and cIMT ($P<0.001$); in the obesity group with HbA1c ($P<0.02$), VCAM-1 ($P<0.02$), MDA ($P<0.0001$), and 8-oxo-DG ($P<0.00001$).
Conclusion
The results show association of serum AGEs with ICAM-1 and HOMA-IR and strong association of sRAGE with VCAM-1, ICAM-1, MDA, and cIMT.
Disclosure
Supported by Grant of FOMIX-GTO (GTO-2012-C03-195211).
DOI: 10.1530/endoabs.37.EP624

EP625

The body distribution of iodine-125 labeled irisin in 10-week-old rats: preliminary data

Ariadna Zybek[1], Marcin Trejter[2], Maciej Zabel[2] & Marek Ruchała[1]
[1]Department of Endocrinology, Metabolism and Internal Medicine, Poznan University of Medical Sciences, Poznan, Poland; [2]Department of Histology and Embryology, Poznan University of Medical Sciences, Poznan, Poland.

Introduction
Irisin is a newly discovered adipo-myokine, that has a significant influence on body metabolism. Available data about this peptide is still insufficient. The aim of the study is to provide some initial information about body distribution of irisin in rats.
Methods
The studied group consisted of 27 10-week-old female Wistar rats, which received intraperitoneally ~0.7 mcCi of iodine-125 labeled irisin. The studied rats were divided on five subgroups: six were decapitated after 15 min, five after 30 min, 1 h and 2.5 h and last six after 5 h. The samples from blood, kidneys, liver, subcutaneous and visceral fat, heart, skeletal muscles, diaphragm, adrenals, brain and cerebellum were taken, scaled and the radiation was measured (counts per minute (CPM)). The same procedure was applied for five rats which received only saline intraperitoneally – control group.
Results
The maximum radiation (CPM/1 g) in the blood was registered 1 h after the injection. At that moment the highest radiation was detected in kidneys. After 1 h the maximum radiation was registered also in liver, heart, and skeletal muscles. In case of brain and cerebellum the maximum point was depicted after 2.5 h. The diaphragm, subcutenaus fat, visceral fat, and adrenals presented very high radiation just after the injection, which decreased rapidly with time. At every point of the study the studied group tissue radiation was significantly higher than in the control group ($P<0.05$).
Conclusions
It may be assumed that intraperitoneally injected irisin has a standard distribution associated with blood perfusion and crosses the blood–brain barrier. There is no specific accumulation in described organs. The initial high radiation of diaphragm, subcutaneous fat, visceral fat and adrenals may be associated with the place of injection, thus is not reliable.
DOI: 10.1530/endoabs.37.EP625

EP626

Obesity and breast cancer – does size matter?

Ioana Armasu[1], Iulia Crumpei[1], Constantin Volovat[2], Alina Daniela Belceanu[1], Georgiana Andreea Constantinescu[1], Mariana Tofan[2], Maria Christina Ungureanu[1], Letitia Leustean[1] & Carmen Vulpoi[1]
[1]Department of Endocrinology, University of Medicine and Pharmacy 'Gr.T. Popa', Iasi, Romania; [2]Victoria Hospital, Iasi, Romania.

Introduction
The epidemic of obesity has risen many health concerns, beneath the metabolic syndrome. One of these problems is the effect of obesity on cancer evolution. Populational studies have shown a direct correlation of BMI with worse prognostic, life quality and occurrence of comorbidities in neoplastic diseases, one of the most studied being breast cancer.
Patients and methods
We retrospectively analysed the evolution of postmenopausal obese and overweight women with non-metastatic breast cancer with antioestrogen treatment (selective oestrogen receptor modulators and/or aromatase inhibitors). From the 235 patients who received this treatment we selected) 62 with regular records of BMI. Excluding criteria were previous hormonal treatment of menopause, diabetes mellitus at the diagnostic, and smoking. Mean age at the diagnostic was 57.5 ± 12 years, mean BMI 28.5 ± 4.6 kg/m^2. Survival was between 3 months and 20 years.
Results
Pearson correlation showed a negative correlation between BMI and survival time ($r=-0.357$, $P=0.04$), however, there were no statistical differences between normal (N), overweight (OW), and obese (O) women respectively (*t*-test N vs OW $P=0.33$. N vs O $P=0.41$, OW vs O $P=0.46$). No modifications of life style could be noticed, at least in the OW and O women, since their weight remained practically unchanged. Women with longer survival were included in a quality of life study and, also all had a slight deterioration of role functions, emotional and cognitive functions, no differences associated with higher BMI could be observed.
Conclusions
Breast cancer is a multifactorial disease. Obesity is considered a predisposing factor, especially in postmenopausal women. However, many studies showed that not the obesity *per se* but that associated with sarcopenia has a most deleterious effect. Our study is limited by its retrospective design and the absence of body composition evaluation but had demonstrated direct association between obesity and a poor survival rate.
DOI: 10.1530/endoabs.37.EP626

EP627

Irisin/leptin ratio, a biological marker of lean/fat mass, may help to identify LMNA-mutated familial partial lipodystrophies

Faiza Bensmaine[1], Kristell Le Mapihan[1], Samuel Bourry[2], Georges Lion[3], Corinne Vigouroux[4], Pascal Pigny[5] & Marie Christine Vantyghem[1,6]
[1]Department of Endocrinology and Metabolism, Lille University Hospital, Lille, France; [2]Department of Radiology, Lille University Hospital, Lille, France; [3]Department of Nuclear Medicine, Lille University Hospital, Lille, France; [4]Saint-Antoine University Hospital, Pierre and Marie-Curie University Paris, Paris, France; [5]Department of Biology, Lille University Hospital, Lille, France; [6]INSERM, U859 Biotherapies for Diabetes, European Genomic Institute for Diabetes, Lille, France.

Irisin is a myokine correlated with lean body mass, despite its association with cardiovascular events (Mantzoros 2014). Increased muscle volume and

lipoatrophy have been reported in female FPLD (Ji JCEM 214). Our aim was to determine whether irisin could help to distinguish certain lipodystrophic obesities from FPLD.
Methods and patients
Circulating irisin levels (EIA Phoenix) were measured in 20 LMNA-related FPLD, 19 normal-weighed controls (H) and 13 obese non-diabetic (OND) patients, and correlated with body composition (DEXA/MRI), and metabolic and inflammatory (CRP, leukocytes CD4) parameters (Clin.gov2009-AO-1169-48).
Results
Irisin medians differed between the three groups (P: 0.0076) and were higher in OND (P: 0.0099) and FPLD (P: 0.047) than in H groups, without difference between FPLD and OND. Irisinaemia, similar between male and female, was positively correlated to lean mass (g)/height^2 ($r=0.51$; $P<0.0001$), BMI, triglycerides ($r=0.45$–0.49; $P<0.001$) and to a lesser extent to insulin, body weight, MRI-intra-abdominal fat mass, MRI-intra-abdominal/MRI-total fat mass, FBG, A1c, cholesterol, and ASAT ($r=0.42$–0.33; $P<0.01$). The ratio 'lean mass/height^2' differed significantly between the three groups ($P<0.0001$) with higher values in OND ($P<0.0001$) and FPLD ($P=0.03$) compared to H groups, without difference between FPLD and OND. Leptinaemia was higher in OND compared to H and FPLD ($P<0.0001$), without difference between these two groups. The ratio «irisin/leptin» differed between the three groups ($P<0.0001$) with higher values in FPLD and H (both $P<0.0001$) compared to OND, without difference between FPLD and H. Irisin was not correlated with leptin and inflammatory parameters.
Conclusion
FPLD is characterized by high irisinemia and low leptinemia, OND by both high leptinaemia and irisinaemia. Irisin is increased in diseases characterised by higher lean mass whatever the amount of fat mass. Irisin/leptin ratio, a biological marker of lean/fat mass, may help to identify FPLD.

DOI: 10.1530/endoabs.37.EP627

EP628

The relation between metabolic syndrome and cognitive decline in type 2 diabetes elderly Tunisian people

Hela Marmouch[1,2], Tasnim Slim[1], Fadia Boubaker[1], Sondes Arfa[1], Manel Jmal[1,2], Hanene Sayadi[1,2] & Ines Khochtali[1,2]
[1]Department of Internal Medecine-Endocrinology, Monastir, Tunisia; [2]Faculty of Medecine, Monastir, Tunisia.

Objective
To determine the relationship between metabolic syndrome (MS) and cognitive decline in type 2 diabetes patients over 65 years age.
Methods
The age of the participants were between 60 and 87 years old. According to NCEP ATP III criteria 30 had MS and 28 had not. Cognitive performance was determined with the use of standardised mini mental test and the mini mental scores (MMS) of the two groups were compared. Apart from the MS we investigated the relationship between MMS and age, gender, educational status, tobacco and alcohol use, the history of acute myocardial infarction (AMI) and stroke, medication use (antihypertensive, insulin, oral antidiabetic, statin) and BMI. Depression, which is a cause of pseudodementia, was also assessed with the use of geriatric depression scale (GDS).
Results
The MMS was low in ten patients (33.3%) in the MS group, and in ten subjects (25%) in the control group. We could not find difference between MMS's of two groups statistically. In this study the MMS was low in subjects with high fasting plasma glucose level, tobacco use, insulin use, advanced age and depression. The GDS's of two groups were similar. There was not difference in the MMS's between patients with high blood pressure, high triglyceride level, low HDL cholesterol level, history of AMI and stroke, low educational status, high BMI and in whom without them. We also could not find difference between MMS's of the patients who use antihypertensives, oral antidiabetics and statins and in whom not using these medications.
Conclusion
The number of elderly people increases in Tunisian, however, cognitive decline related to diseases also increases. The establishment of the risk factors, which affect the cognitive functions and prevention of them in elderly, would prevent the cognitive decline, one of the important causes of mortality and morbidity in today's world.

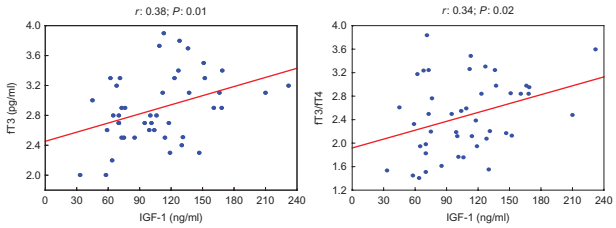
DOI: 10.1530/endoabs.37.EP628

EP629

IGF-1 levels correlate with T_3 status in chronic heart failure outpatients: preliminary data

Vincenzo Triggiani[1], Massimo Iacoviello[2], Marta Leone[2], Vito Angelo Giagulli[1], Edoardo Guastamacchia[1], Andrea Salzano[3], Emanuele Bobbio[3], Michele Arcopinto[4] & Antonio Cittadini[3]
[1]Unit of Endocrinology, Interdisciplinary Department of Medicine, University of Bari, Bari, Italy; [2]Unit of Cardiology, Department of Emergency and Organs Transplantation, University of Bari, Bari, Italy; [3]Department of Translational Medical Science, Federico II University, Naples, Italy; [4]Department of Cardiac Surgery, IRCCS, Policlinico S. Donato, Milan, Italy.

Background
A variety of hormones may be down-regulated in CHF patients. Impaired activity of the GH/IGF-1 axis has been described and is associated with poor clinical status and outcome. Moreover, a decrease in serum T_3 is correlated to the severity of the heart disease as assessed by the NYHA classification. Aim of this study was to evaluate a possible correlation between IGF-1 levels and T_3 status in a cohort of CHF outpatients.
Materials and methods
Forty-eight consecutive CHF outpatients (79% males; age 61 ± 13 years; BMI 29 ± 5 kg/m^2; NYHA class 2.3 ± 0.6; 47% with ischemic disease), in stable clinical conditions from at least 30 days, in conventional electrical and medical therapy (87% taking ACE-inhibitors or angiotensin receptor blockers, 96% β blockers, 96% diuretics, 72% anti-aldosterone drugs, 13% digitalis, 14% nitrates), were enrolled in the study. They were submitted to physical examination, electrocardiography and echocardiography. Blood samples were drawn to assess renal function, Na^+, haemoglobin, NT-proBNPs, fT_3, fT_4, TSH, IGF-1, testosterone, DHEA and insulin levels.
Results
At univariate analysis, IGF-1 showed a direct correlation with fT_3 and the same was found between IGF-1 levels and fT_3/fT_4 ratio, whereas no correlation was found between IGF-1 and the other measures. Furthermore, at multivariate analysis, including also NHYA class, fT_3 was the only independent predictor of IGF-1 levels. The figure below shows a direct correlation between IGF-1 levels and both fT3 levels and fT_3/fT_4 ratio.
Conclusions
Impaired IGF-1 and fT_3 status may both represent a derangement strictly correlated to the severity of the clinical condition in CHF.



DOI: 10.1530/endoabs.37.EP629

EP630

Diet relationship with the metabolic syndrome's elements

Raluca-Monica Pop, Ionela Pascanu, Grigore Dogaru & Marian Pop
University of Medicine and Pharmacy Tg Mures, Tirgu-Mures, Romania.

Background
Diet modification is an important part of the metabolic syndrome's management but there is limited data regarding a direct relationship between food groups and the metabolic profile.
Aim
Evaluation of the influence of food groups on the elements of metabolic syndrome in a group of subjects with abdominal obesity.

Material and methods
A cross sectional study was conducted in the Endocrinology Outpatient Clinic between February 2013 and April 2014. A sample of 290 subjects was analysed. Inclusion criteria: abdominal obesity defined according to IDF definition. Exclusion criteria: treatment for the metabolic syndrome's elements. Variables: age, sex, environment, waist, BMI, blood pressure, blood glucose, triglycerides, HDL cholesterol, food pyramid.
Method
Anthropometric evaluation, fasting blood sample, blood pressure measurement, food pyramid constructed based on an adapted food frequency questionnaire with 126 items analyzed with a web-based application especially developed. Statistical analysis used GraphPad Prism v. 5 and SPSS v17 with a level of significance $\alpha = 0.05$.
Results
Mean age was 50.6 ± 13.1 years with a sex distribution F:M 6.8:1 with the majority of subjects coming from urban areas (68.27%). In multiple regression analysis, the food pyramid elements explain 6.26% of the triglycerides variation ($P = 0.02$), 3.14% of the HDL cholesterol ($P = 0.31$), 4.55% of the blood glucose ($P = 0.09$), 7.25% of the blood pressure value ($P = 0.08$) and 5.75% of the waist circumference ($P = 0.01$). All of the metabolic syndrome elements are correlated with waist circumference and significantly influence each other's variability.
Conclusion
The main food groups explain a small percentage of the metabolic syndrome's elements underlying the need for a more detailed dietary evaluation to define specific patterns associated with increase cardio-vascular risk.
Disclosure
Project partly supported through an Internal Research Grant of University of Medicine and Pharmacy Tirgu Mures, no. 13/30.01.2013.

DOI: 10.1530/endoabs.37.EP630

EP631

A common variant (rs9939609) in the fat mass and obesity associated gene is not associated with obesity, but associated with metabolic syndrome in girls among adolescents

Nilgun Col Araz[1], Mustafa Araz[2] & Muradiye Nacak[3]
[1]Department of Pediatrics, Gaziantep University Hospital, Gaziantep, Turkey; [2]Department of Endocrinology, Gaziantep University Hospital, Gaziantep, Turkey; [3]Department of Pharmacology, Gaziantep University Hospital, Gaziantep, Turkey.

Introduction
Fat mass and obesity associated (FTO) gene was the first susceptibility locus for obesity identified by genome wide association studies. The association of the FTO gene with obesity and metabolic syndrome is conflicting in both adults and adolescents. The aim of this study was to examine the role of the FTO gene variant rs9939609 as a candidate gene for obesity and metabolic syndrome, among Caucasian adolescents in South-eastern Turkey.
Methods
One hundred obese adolescents and 100 healthy controls were included. Obesity and metabolic syndrome were defined according to the international obesity task force's international standards and to the NCEP criteria, respectively. Rs9939609 polymorphism in FTO gene was genotyped by PCR–SNaPshot.
Results
The prevalence of metabolic syndrome was 60%. For *FTO* T/A polymorphism, the distribution of T/T, T/A, and A/A genotypes was 32.0, 48.0 and 20.0% in obese children compared with 41.0, 36.0 and 23.0% in controls ($P > 0.05$). The allele frequency of T and A was 56.0, 44.0% in patients compared with 59.0, 41.0% in controls ($P = 0.306$). There was no significant difference in genotype and allele frequencies between obese patients and controls. Also, the distribution of genotypes and alleles was not different in patients with and without MetS. However, the prevalence of metabolic syndrome in female patients with A allele carriers was more frequent than with non-carriers (carriers: 23/36, 63.9%; non-carriers: 4/14, 28.6%; $\chi^2 = 5.062$; $P = 0.024$).
Conclusion
We could not confirm the FTO rs9939609 variant as an obesity and metabolic syndrome susceptibility gene in adolescents, but we observe an association with metabolic syndrome in girls. There is a need to explain the possible gender effect of FTO gene polymorphism.

DOI: 10.1530/endoabs.37.EP631

EP632

The relationship between haemoglobin and BMI in overweight and obese patients

Ayse Gozkaman[1], Yildiz Okuturlar[2], Meral Mert[3], Ozlem Harmankaya[1] & Abdulbaki Kumbasar[1]
[1]Department of Internal Medicine, Uludag University School of Medicine, Bursa, Turkey; [2]Department of Internal Medicine, Bakirkoy Dr Sadi Konuk Education and Research Hospital, Istanbul, Turkey; [3]Department of Endocrinology and Metabolism, Bakirkoy Dr Sadi Konuk Education and Research Hospital, Istanbul, Turkey.

Introduction
Both overweight/obesity and central obesity were inversely associated with anemia in the studies. In our study, we aimed to determine the relationship between different haemoglobin (Hb) levels and BMI.
Materials and methods
A total of 146 patients (131 (89.1%) female and 15 (10.2%) male) were enrolled in the study. Patients were divided into five groups namely group-1 (Hb $\leq$7 g/dl), group-2 (7 g/dl $<$ Hb $\leq$10 g/dl), group-3 (10 g/dl $<$ Hb $\leq$12 g/dl), group-4 (12 g/dl $<$ Hb $\leq$14 g/dl) and group-5 (14 g/dl $<$ Hb). Complete blood count, BMI, biochemical parameters, iron and iron binding capacity (IBC), ferritin, vitamin B12 and folic acid levels of all patients were measured.
Results
BMI levels were found to be significantly different in each five groups. These differences were found between group-1 and 3 ($P = 0.0001$), group-2 and 3 ($P = 0.0001$), group-3 and 4 ($P = 0.011$) and group-3 and 5 ($P = 0.032$). A positive correlation was found between BMI and Hb ($r = 0.199$, $P = 0.017$). There was a positive correlation between BMI and mean corpuscular volume (MCV) ($r = 0.298$, $P = 0.001$), negative correlation between BMI and IBC ($r = -0.223$, $P = 0.011$).
Conclusion
In obese patients, adverse effects on quality of life, exercise capacity and cardiovascular diseases of the anemia should be considered while planning lifestyle changes in obesity.

DOI: 10.1530/endoabs.37.EP632

EP633

Advanced glycation end products, their receptors RAGE and AGER-1 and their association with insulin resistance and inflammation in obese and non-obese young subjects

Sofia Torres-Graciano[1], Etzabel Villegas-Rodriguez[1], Martha E Fajardo-Araujo[1], Juan Manuel Malacara[1], Antonio E Rivera-Cisneros[2] & Ma Eugenia Garay-Sevilla[1]
[1]Departmen of Medical Science, University of Guanajuato, Leon, Gto., Mexico; [2]Decanato de Salud, Universidad Autónoma de Guadalajara, Guadalajara, Jal., Mexico.

In obesity the combined effects of enhanced food consumption, enhanced oxidative stress and inflammation could increase levels of advanced glycation end products (AGEs) and the action of their receptors.
Objective
To study circulating levels of AGEs, soluble RAGE and AGER-1 and their association with insulin resistance and inflammation in young subjects with obesity and normal weight.
Material and methods
We conducted a cross-sectional study in obese Young ($n = 80$) and normal weight ($n = 80$). We calculated the BMI according to Cole *et al*., and the consumption of AGEs in the diet (dAGEs) with the tables of Uribarri *et al*. We measured glucose, lipid profile, insulin, HOMA-IR, TNF-α, serum AGEs (CML) and sRAGE. In a subsample of 27 subjects with normal weight and 21 subject with obesity we also measured the expression of RAGE and AGER1 by qPCR.
Results
We studied a total of 160 subjects (16 ± 1 years old) and 55% females. The group with obesity show higher levels of triglycerides ($P < 0.003$), insulin ($P < 0.001$), HOMA-IR ($P < 0.001$) and TNF-α ($P < 0.04$). In the groups with obesity and consumption of AGEs $>$9000 KU/day we found higher levels of insulin ($P < 0.0001$), HOMA-IR ($P < 0.01$) and sRAGE ($P < 0.04$). CML was associated with HOMA-IR ($P < 0.02$) and TNF-α ($P < 0.03$). In the sample were we studied the expression of cellular receptors we found higher expression of AGER-1 in the obesity group ($P < 0.02$) and association of AGER-1 with weight ($P < 0.02$) and dAGE ($P < 0.02$) and RAGE with physical activity (t-2.14; $P < 0.03$).

Conclusion
The results show higher insulin resistance and inflammation in the subjects with obesity, also association of CML with insulin resistance and TNF-α; and higher expression of AGER1 in the obesity group.
Disclosure
Supported by University of Guanajuato DAIP 2013.
DOI: 10.1530/endoabs.37.EP633

EP634

Bone and calcium markers in relation to cardiovascular risk in patients with osteoporosis

Carmen Gabriela Barbu[1,2], Suzana Florea[3], Anca Sirbu[1,2], Alice Albu[1,2], Sorina Martin[1,2] & Simona Fica[1,2]
[1]Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; [2]Elias Hospital Endocrinology Department, Bucharest, Romania; [3]Elias Hospital Core Laboratory, Bucharest, Romania.

Aim of the study was to evaluate the relationship between biochemical bone turnover markers, calcium homeostasis parameters and the cardiovascular risk in patients with osteoporosis.
Materials and methods
Subjects were 246 patients (mean age of 56.64) diagnosed with osteoporosis referred to the endocrine department of Elias Hospital, between 2009 and 2013, and who agreed with the terms of the study. Data collection consisted of clinical evaluation, physical exam and biochemical routine blood tests and hormones and the parameters of calcium homeostasis needed for differential diagnosis of osteoporosis. Osteoporosis was diagnosed based on the WHO criteria and metabolic syndrome based on the IDF 2007 guidelines. In order to evaluate the relationship between calcium and bone parameters and cardiovascular risk, we used metabolic syndrome as the criteria to segregate the subjects in control group (without Mets) and study subjects (with Mets).
Results
Serum intact PTH levels were significantly higher in Mets group: 76.2 (40.8) pg/ml, comparing to 65.6 (42.8) pg/ml in control group ($P<0.01$). No other calcium or bone biochemical marker (serum calcium, 24 h calciuria, serum osteocalcin, 25HO vitamin D, serum betacrosslaps) was significantly different across the study groups.
Conclusion
Hyperparathyroidism, either secondary or primary is frequent among patients with osteoporosis. Increased level of parathyroid hormone was found to be associated with increased risk in cardiovascular disease in our patients with osteoporosis suggesting that, beside the bone aspects, there may be also some other metabolic effects of the excess of the parathyroid hormone.
DOI: 10.1530/endoabs.37.EP634

EP635

Therapeutic education contributes to minimise excess weight in Prader-Willi syndrome

Roxana Stefan[1], Cristina Rusu[2], Ioana Armasu[3], Alina Belceanu[3], Elena Braha[2], Carmen Gorduza[3], Bogdan Mihai[4], Cristina Lacatusu[4], Mihaela Negru[3] & Carmen Vulpoi[3]
[1]Clinic Center Providenta, Iasi, Romania; [2]Department of Genetics, Iasi, Romania; [3]Department of Endocrinology, Iasi, Romania; [4]Department of Diabetes, Nutrition and Metabolic Disease, Iasi, Romania.

Introduction
Prader-Willi syndrome (PWS) is a complex genetic disorder characterised by hyperphagia with progressive obesity, dysmorphic features, hypotonia, mental retardation, behavioural abnormalities and endocrine dysfunctions as hypogonadism and growth hormone (GH) deficiency. PWS is the most commonly identified genetic cause of obesity.
Methods
We reviewed five cases of confirmed PWS (three female and two male patients, aged between 8 and 32 years old) evaluated at the Endocrinology Department of Iaşi between January 2008 and July 2013. Clinical and hormonal data were documented.
Results
All patients had specific clinical features of PWS and genetic confirmation. They were all born in non-sanguine couples, four of them with low birth weight. After the first year of life they presented hyperfagia with rapid and important weight gain, except for one case where hyperphagia began in adolescence (at 13 years of age). The major weight gain was until late adolescence ($>+6$ S.D.). Nutritional counselling, with detailed information about diet, exercise, and subsequent adverse consequences of obesity, was offered to patients and family in order to ameliorate their eating behaviour. After that, the three patients that reached adulthood achieved a mean weight at $+1.5$ S.D. (under rigorous alimentation). Paradoxally, all patients had a higher height than expected (mean $+1.5$ S.D.) in childhood and adolescence, even though three of them had low IGF1. Two patients had their first endocrinological examination in adulthood and presented a satisfactory final height (>155 cm).
Conclusions
Therapeutical education of the family, performed as early as possible, is an important determinant of the disease evolution and diminishes the potential weight gain. Although most patients with PWS have morbid obesity it seems that caregivers involvement in weight management may lead to favorable results.
DOI: 10.1530/endoabs.37.EP635

EP636

The use of intermittent 7.5 mg tolvaptan on an out-patient basis for SIADH: a retrospective audit from a tertiary cancer hospital

Mohit Kumar, Lakshminarayanan Pichaipillai, Peter Trainer & Claire Higham
Department of Endocrinology, Christie Hospital, Manchester, UK.

Tolvaptan (a V2 receptor antagonist) is licensed for correction of hyponatraemia in patients with SIADH at an initial dose of 15 mg od. Data in oncology patients with SIADH suggest 7.5 mg can safely and effectively increase sodium levels where 15 mg can on occasion lead to too rapid a correction. Recommendations suggest a repeat sodium taken at 4–6 h. We retrospectively assessed the safety and efficacy of intermittent out-patient dosing with 7.5 mg tolvaptan. Pharmacy records and casenotes were interrogated to find all patients given out-patient prescriptions for tolvaptan between April 12 and January 15. 15 doses were administered in a total of four patients (three men, one female; mean age 63 years). All had biochemically confirmed SIADH secondary to small cell lung cancer, had received fluid restriction and demeclocycline prior to tolvaptan as inpatients and were euvolaemic. All patients were also receiving therapy for the primary malignancy concurrently. Indications for treatment were symptomatic hyponatraemia or downward trending sodium. Mean pre-out-patient tolvaptan sodium was 126 mmol/l (range 122–128). Mean first sodium post-tolvaptan was 133.6 mmol/l (range 128–139), with mean increase 7.6 mmol/l. Timing of repeat sodium ranged from 6 h to 6 days. On eight occasions a repeat sodium was done at 6 h – mean sodium rose from 125.75 (122–128) to 132 mmol/l (128–137). The largest rise was 10 mmol/l at 6 h. No adverse events were encountered. One patient died due to progressive malignancy.
Conclusion
Outpatient use of single 7.5 mg doses of tolvaptan is effective at raising serum sodium in oncology patients with SIADH, thus potentially reducing admissions with economic (dose and bed-stay) and patient benefits. There were no adverse effects encountered in the small patient cohort analysed, but robust protocols need to be in place to prevent complications. Improvements need to be made in checking a 6-h sodium.
DOI: 10.1530/endoabs.37.EP636

EP637

Type 2 diabetes mellitus and obesity: the possibilities of antihypertensive therapy

Tatiana Shebuniaeva & Marina Sergeeva-Kondrachenko
SEI APE 'Penza Postgraduate Medical Institute' of Ministry of Health of Russia, Penza, Russia.

Purpose
To evaluate the effectiveness of a combined antihypertensive therapy in treating arterial hypertension (AH) in patients suffering from diabetes mellitus (Type 2 DM) on different stages of obesity.
Materials and methods
80 patients suffering from Type 2 DM and AH on different stages of obesity underwent a monitoring. Depending on the stage of obesity, the patients were divided into three groups. The groups were comparable by age, sex, AH stage. The patients received comparable oral hypoglycemic agents. On voluntary basis the patients did not receive antihypertensive agents 5–7 days before being included into the research. Aiming at correcting AH, the patients received PRESTANCE (the combination of perindopril and amlodipine) in the doses of: 5/5, 5/10,10/5,10/10 during 12 months. Daily monitoring of AP (ABPM) was conducted with the help of a non-invasive portable system, HbA1c was determined. The blood glucose was determined on an empty stomach and 2 h after meals. The treatment of results was carried out with the use of STATISTICA pack.
Results
The average age of the patients was 57.5 ± 3.4 years, women prevailed – 75%. The average ABP value was: 168 ± 11 and 105 ± 7 mmHg – for systolic and diastolic blood pressure respectively. By week 12 observations of 85% patients from group 1 reached the target ABP and was retained until week 48, 78% patients from group 2 reached the target values of ABP and 72% patients from group 3 retaining it until observation week 48. By week 12 of observation in each group was significantly ($P < 0.01$) decreased the level of total cholesterol plasma, LDL cholesterol, triglycerides, fasting and postprandial blood glucose, HbA1c and BMI showed a decrease. All the patients participating in the research, showed good tolerance of PRESTANCE.
Conclusions
The combination of perindopril and amlodipine provides sustainable management of ABP in patients with Type 2 DM and different obesity stages, is well tolerated, has a beneficial effect on carbohydrate and lipid metabolism, leads to weight decrease.

DOI: 10.1530/endoabs.37.EP637

EP638

Serum adipokine profile and adiponectin gene expression in neck adipose tissue in premenopausal and postmenopausal women

Vlatka Pandzic Jaksic[1], Danijela Grizelj[1], Drago Boscic[1], Marko Ajduk[1], Tomislav Kelava[2], Danka Grcevic[2], Maruska Marusic[1], Rajko Kusec[1,2] & Ozren Jaksic[1,2]
[1]Dubrava University Hospital, Zagreb, Croatia; [2]School of Medicine, Zagreb, Croatia.

Adipokines are an important contributor to the circulatory milieu of the body. The spectrum of adipokines changes as dysfunctional features of adipose tissue develop and the menopause is a time when an impairment of metabolic balance appears. The aim of this study was to examine several serum adipokines and adiponectin gene expression in subcutaneous and deep neck adipose tissue in women. Samples of serum, subcutaneous and deep neck adipose tissue were taken in 41 (12 premenopausal and 29 postmenopausal) women undergoing routine thyroid or vascular surgery. Serum adiponectin, leptin, omentin-1, monocyte chemoattractant protein-1 (MCP-1), fibroblast growth factor 21 (FGF21), retinol binding protein 4 (RBP4), insulin, glucose, triglycerides, HDL-cholesterol and C-reactive protein were determined. HOMA-IR was calculated and anthropometric measurements were performed. Adiponectin gene expression in adipose tissue samples was analysed by RQ–PCR method. Serum adiponectin and omentin-1 were negatively and leptin was positively associated with body weight, BMI and waist and neck circumference. RBP4 correlated with waist circumference and triglycerides. Leptin also was associated positively and omentin-1 negatively with triglycerides. FGF21 correlated with glucose and HDL-cholesterol. Omentin-1 negatively correlated with RBP4 and positively with serum adiponectin. Both serum adiponectin and omentin-1 were negatively associated with leptin. MCP-1 correlated only with RBP4. FGF21 didn't correlate with other adipokines. Subcutaneous and deep adiponectin gene expressions were negatively associated with insulin, HOMA-IR and RBP4 but positively with omentin-1. Comparisons between premenopausal and postmenopausal group yielded significant differences in insulin, HOMA-IR, MCP-1 and RBP4. These results confirm multiple associations of various adipokines with metabolic parameters and secretory features of the neck adipose tissue depot. However, they also suggest that some adipokines cluster in specific profiles with potential particular biologic functions that should be further elucidated.

Disclosure
The study was supported by the Ministry of Science, Education and Sports of the Republic of Croatia Grant No. 198-1980955-0953.

DOI: 10.1530/endoabs.37.EP638

EP639

Impact of visceral adiposity on blood pressure in normotensive people: a study among health staff

Nayananjani Karunasena[1,2] & Uditha Bulugahapitiya[1]
[1]Diabetes and Endocrine Unit, Colombo South Teaching Hospital, Colombo, Sri Lanka; [2]Academic Unit of Diabetes, Endocrinology and Metabolism, Department of Human Metabolism, University of Sheffield, Sheffield, UK.

Background
Obesity is often complicated by cardiovascular and atherosclerotic disease. Central or visceral obesity is known to be associated with hypertension and cardiovascular disease. Even though BMI is a good indicator of obesity in epidemiological studies, it does not differentiate between lean and fat mass. Furthermore waist circumference (WC) and visceral fat percentages are better indicators of visceral obesity. Aim of this study was to investigate the correlation of blood pressure with different measures of obesity in normotensive people.
Method
A cross sectional study carried out among the health staff in a tertiary care setting. 452 were screened among all categories of health staff and 410 were enrolled for the study excluding the known hypertensive people. Body fat and visceral fat percentages were estimated using bioelectrical impedance analysis (BIA) method.
Results
Out of the 410 subjects 63% ($n = 258$) were females and 37%($n = 152$) were males. Mean age of the study population was 41.7 ± 9.4 years. Mean systolic blood pressure (SBP) was 121 ± 13 mmHg among males and 118 ± 12.5 mmHg among females. Mean diastolic blood pressure (DBP) was 77.82 ± 8.9 and 75.3 ± 9.0 mmHg among males and females respectively. In females both SBP ($r = 0.268$, $P < 0.001$) and DBP ($r = 0.209$, $P = 0.001$) showed strongest correlation with WC compared to visceral fat percentage, total fat percentage and BMI. In females there was a good but less strong correlation with visceral fat percentage as well (SBP $P = 0.001$, DBP $P = 0.017$). In males both SBP ($r = 0.225$, $P = 0.006$) and DBP ($r = 0.180$, $P = 0.029$) showed strongest correlation with total body fat percentage compared to the other measures of obesity.
Conclusions
Among females both systolic and diastolic blood pressures are significantly affected by increased visceral adiposity as reflected by correlation with waist circumference and visceral fat percentage. However, among males blood pressure is not significantly affected by the visceral adiposity.

DOI: 10.1530/endoabs.37.EP639

EP640

Metabolic consequences of abdominal obesity: about 105 Algerian obese patients

Aziza Smili[1], Remini Djida[1], Djamila Meskine[2], Eh Ahmed Koceir[3] & Yacine Soltani[1]
[1]Endocrinology Laboratory, Organisms Biology and Physiology Department, FSB, USTHB, Algies, Algeria; [2]Departement of Endocrinology, EPH Bologine Ibn Ziri, Algies, Algeria; [3]Bioenergitic and Intermediate Metabolism Laboratory, FSB USTHB, Algies, Algeria.

Introduction
The frequency of obesity is increasing in Algeria, insulin resistance is one of the consequences pathological of the abdominal obesity. The purpose of this work is to study the implication of the abdominal obesity in the insulinorésistance and the complications which arise by the latter.
Materials and methods
The study is realised on 105 obese (85 women and 20 men) (BMI > 30) and 55 thin (40 women and 15 men) with mean age 37.60 ± 1.18 and 31.03 ± 1.73 years respectively. Glycaemia, lipidaemia, cortisol, insulin and the leptin are analysed. The resistance and the sensibility in the insulin are estimated by the index HOMA-R and QUIKI. The obesity android was held in the criteria of the US NCEP ATP III Defines by a WHR ≥ 0.85 for women and WHR ≥ 1.00 for men.

Results
92% sick suffer from an obesity android associated with critical insulin resistance (HOMA-IR: HOMAR-R: 12.88 ± 1.03 vs 5.17 ± 0.86 $P < 0.001$.QUIKI: 0.29 ± 0.002 vs 0.31 ± 0.002; $P < 0.001$). Plasma cortisol and leptin were higher in obese group by 16% ($P < 0.05$) and 75% ($P < 0.001$) respectively, compared to control group. According to US NCEP ATP III 52 obese (50%) show lipid disturbances associated to dyslipidaemia and metabolic syndrome. Our results show a negative correlation between QUIKI and TT ($r = -0.29$ $P = 0.02$).
Conclusion
Abdominal obesity associated with metabolic disorders have led to a metabolic syndrome according to US NCEP-ATP III and a physiological stress which stimulated the secretion of cortisol. Despite the significant increase of leptin, known to inhibit adrenal axis. These data suggest that leptin resistance is developed in obese subjects.

DOI: 10.1530/endoabs.37.EP640

EP641

Body composition in HIV-infected patients under combined antiretroviral therapy over 5 years

Inês Grenha[1,4], Joana Oliveira[1,4], Eva Lau[1,4], Romana Vieira[2,4], Rosário Serrão[3,4], António Sarmento[3,4], Davide Carvalho[1,4] & Paula Freitas[1,4]
[1]Endocrinology, Diabetes and Metabolism Department, Centro Hospitalar São João, Porto, Portugal; [2]Reumathology Department, Centro Hospitalar São João, Porto, Portugal; [3]nfectious Diseases Department, Centro Hospitar São João, Porto, Portugal; [4]Faculty of Medicine of University of Porto, Porto, Portugal

Introduction
HIV infection and combined antiretroviral therapy (cART) have been associated with lipodistrophy and changes in body composition. However, there are few studies on body composition evolution of HIV-infected patients, under cART.
Aims
To evaluate the evolution of body composition in HIV-1 infected patients under cART over 5 years.
Methods
Retrospective, observational study in a cohort of HIV-infected patients on cART. Evaluation of clinical data and body composition (total fat mass, upper-limbs fat mass, lower-limbs fat mass, trunk fat mass and fat-free mass) by DXA (whole-body dual-energy X-ray absorptiometry).
Results
A total of 257 patients were evaluated, with a mean age of 45.98 (11.51) years. 63% were males. The median duration of HIV infection was 7.92 (IQR: 3.90) years and the median duration of cART was 6.61 (IQR: 3.9) years. Males had a baseline mean BMI of 24.37 (22.17–26.91) Kg/m^2. Over the five years, there was a significant increase in their % of upper limbs, lower limbs, trunk and total fat mass. At baseline, women had a mean BMI of 25.33 (21.92–29.18) Kg/m^2. Women showed significant decrease in their % of lower limbs fat mass and an increase in % of trunk fat mass; % of total fat mass increased during the first two years and decreased since then. No differences were found regarding fat mass ratio, in both genders. During the five years of follow-up period, man showed a decrease of total fat-free mass and increase of upper-limbs fat-free mass; significant changes were also observed in lower-limbs and trunk fat-free mass distribution. Women also showed significant changes in total, lower-limbs, upper-limbs and trunk fat-free mass during follow-up.
Conclusion
Over the 5 years, there were significant changes in body composition, in HIV-infected patients on cART. Different from women, men showed a sustained increase in % of fat mass of all segments evaluated.

DOI: 10.1530/endoabs.37.EP641

EP642

Patients' expectations and post-bariatric surgery satisfaction

Susana Garrido, Isabel Silva, Luísa Gonçalves, Ana Rita Caldas & M Helena Cardoso
Serviço de Endocrinologia, Diabetes e Metabolismo, Hospital de Santo António, Centro Hospitalar do Porto, Porto, Portugal.

Introduction
Treatment satisfaction is simultaneously a cause and consequence of the success of bariatric surgery – not only it is a reflection of the efficacy of treatment, it also enhances weight loss. A questionnaire that evaluates this variable has recently been created and validated by the authors (Post-Bariatric Surgery Satisfaction Questionnaire).
Objectives
To identify patients' expectations regarding bariatric surgery; to identify the domains that contribute to the degree of satisfaction after bariatric surgery.
Methods
Patients submitted to bariatric surgery who presented to our Obesity Outpatient Clinic between June and December/2013 were asked to complete two questionnaires – Patients' Expectations Questionnaire and Post-Bariatric Surgery Satisfaction Questionnaire (22 items, five-point scale – 1 – very dissatisfied, 5 – very satisfied). Demographic and clinical data were also collected.
Results
A total of 86 patients were included (67% submitted to laparoscopic gastric bypass and 33% to adjustable gastric banding): 86% female, median age 50 years (min–max = 23–73), median follow-up time since surgery 37 months (min–max = 1–220). Actual and idealized BMI of patients was 31.7 kg/m^2 and 27.7 kg/m^2, respectively. Actual and idealized percentage of excess BMI lost was 68.8 and 85.1%, respectively. The majority of the patients selected the items 'reduce weight' (98.8%), 'improve health' (98.8%), 'be able to choose clothing I like' (91.9%) and 'improve self-esteem' (91.9%). Patients were satisfied to very satisfied in all analyzed items (median score between 1.0 and 2.0). However, 34.9% of patients feel dissatisfied to very dissatisfied with their 'naked physical appearance', and 12.8% with 'the need of chronic medication'. 91.9% of the patients would recommend surgery to others and 90.1% of patients would undergo surgery again.
Conclusion
Patients were satisfied to very satisfied in all items tested, despite having unrealistic expectations. It is essential to assess what affects patients' satisfaction in order to understand their behavior and optimize our intervention.

DOI: 10.1530/endoabs.37.EP642

EP643

Insulin resistance does not play a major role in lipid and apolipoprotein profile in obese women

José Silva-Nunes[1,2], Miguel Brito[2] & Luísa Veiga[2]
[1]Endocrinology Department, Curry Cabral Hospital – Lisbon's Central Hospital Group, Lisbon, Portugal; [2]Escola Superior de Tecnologia da Saude de Lisboa, Lisbon, Portugal.

Background
Obesity is associated with increased atherogenesis through alterations in lipids, among other potential factors. Some of those abnormalities might be mediated by insulin resistance (IR).
Aims
To compare lipid and apolipoprotein profile between lean and obese women; to evaluate the influence of IR on lipid and apolipoprotein profile, in obese women.
Methods
We studied 112 obese and 100 normal-weight premenopausal women without known cardiovascular disease. Both groups were characterized for anthropometrics and a fasting blood sample was collected for assessment of glucose, insulin, triglycerides, cholesterol (total, LDL and HDL), and apolipoproteins A-I, A-II, B, C-II, C-III, and E; IR was assessed by the homeostatic model assessment (HOMA-IR). We compared lipids between obese and lean women; we looked for correlation of those levels with anthropometrics and IR (independently from anthropometrics) in obese women.
Results
Obese women were characterized by mean age = 34.6 ± 8.3 years, BMI = 43.6 ± 7.9 kg/m^2, waist circumference (Wc) = 117.5 ± 15.1 cm, and HOMA-IR = 4.28 ± 3.5. Lean women (age = 34.2 ± 8.3 years, BMI = 21.4 ± 1.7 kg/m^2, Wc = 71.7 ± 5.8 cm, and HOMA-IR = 1.21 ± 0.76) presented with significantly lower levels of total cholesterol ($P = 0.001$), LDL-cholesterol ($P < 0.001$), and triglycerides ($P < 0.001$); they presented higher levels of HDL-cholesterol ($P < 0.001$), Apo A-I ($P < 0.001$) and Apo A-II ($P = 0.037$). HOMA-IR showed no significant association with apolipoproteins. HOMA-IR was inversely associated with HDL-cholesterol ($P = 0.048$; $r = -0.187$) but that association disappeared when we adjusted for waist circumference. Only triglycerides were directly associated with HOMA-IR ($P < 0.001$; $r = 0.343$) independently from anthropometrics.

Conclusion
We confirm that obese women present worst lipid and apolipoprotein profile. However, with the exception for triglycerides, insulin resistance *per se* does not play a major role in lipid and apolipoprotein abnormalities observed in obese women.

DOI: 10.1530/endoabs.37.EP643

EP644

VEGFA expression is regulated by 17β-oestradiol and its receptors (ESR1 and ESR2) on 3T3-L1 adipocytes

Luciana Fatima, Raquel Campello & Ubiratan Machado
Department of Physiology and Biophysics, Institute of Biomedical Sciences, University of São Paulo, Sao Paulo, Brazil.

Introduction
VEGFA is considered the main angiogenic factor in adipose tissue. It is believed that a low angiogenic capacity may decrease the adipogenic potential and consequently promotes adipocyte hypertrophy, which in turn, is closely related to insulin resistance (IR). Oestradiol (E_2) is a regulator of the VEGFA gene and a protector against obesity. However nothing is known about the E_2 effects on VEGF adipocyte production, and its consequence for cellular sensitivity and much less about the adjacent molecular mechanisms. Thus, the aim of the present work was to investigate the role of E_2 on the VEGFA expression determining the participation of the estrogen receptors ESR1 and ESR2 in this process.
Methods
Differentiated 3T3-L1 adipocytes were treated (24 h) with 10 e 100 nmol/l of 17β-E_2 and/or selective ESR1-agonist PPT, ESR1-antagonist MPP, ESR2-agonist DPN and ESR2-antagonist PHTPP. We analyzed VEGFA mRNA and protein expression by real time PCR and Western blotting, respectively.
Results
E_2 enhanced VEGFA mRNA and protein (20–30%) expression at 10 and 100 nmol/l. Treatment with PPT enhanced VEGFA expression ($\sim$30%) in the absence or presence of E_2. However treatment with ESR2 agonist DPN didn't change VEGFA expression. In addition, the ESR1-antagonist MPP or the ESR2-antagonist PHTPP alone were not able to change the VEGFA expression, but in the presence of E_2 the VEGFA expression was increased (20–30%) in both treatments as compared to control.
Conclusion
The present results reveal that E_2 induced VEGFA production in adipocytes, in part, via activation of ESR1 receptor. However, there is evidence of co-regulation of both receptors, since in the absence of ESR1, high dose of E_2 was able to induce VEGFA expression. Taken together, the increased VEGFA production induced by E_2 in adipocytes can improve the local angiogenesis, protecting the adipose tissue from obesity-induced hypoxia, and consequently, from insulin resistance.
Disclosure
This work was supported by FAPESP #2012/04831-1 #2013/03343-6.

DOI: 10.1530/endoabs.37.EP644

EP645

Time-of-day-dependent rhythms in the transcriptional responsiveness of the rat heart to triiodothyronine

Rodrigo Peliciari-Garcia[1], Rafael Prévide[1], Martin Young[2] & Maria Tereza Nunes[1]
[1]Department of Physiology and Biophysics, Institute of Biomedical Sciences-I, University of Sao Paulo, Sao Paulo, SP., Brazil; [2]Division of Cardiovascular Diseases, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA.

Myocardial gene expression and metabolism fluctuate over the course of the day, in association with changes in energy supply and demand. Recently, time-of-day-dependent oscillations in myocardial processes have been linked to the intrinsic cardiomyocyte circadian clock. Triiodothyronine (T_3) is an important modulator of cardiac form and function. The genomic actions of T_3 are triggered after its interaction with thyroid hormone nuclear receptors that often dimerized with RXR or RORA. Some target proteins, such as PDK4, are regulated not only by the cardiomyocyte circadian clock, but also by T_3, suggesting a potential interrelationship between the two mechanisms. Circulating levels of T_3 and its intermediates exhibit a time-of-day-dependent oscillation. However, whether the sensitivity of T_3 responsive tissues oscillate in a time-of-day-dependent manner is unknown. Thus, the purpose of the present study was to investigate whether the heart exhibits a diurnal variation in T_3 responsiveness, at a transcriptional level, and/or whether T_3 impacts the circadian clock in the heart. For this, euthyroid (C) male Wistar rats were divided in two groups: vehicle or T_3 (supraphysiological dose), administered 4 h prior each ZT. The animals were euthanized at the respective Zeitgeber Times, during 24 h. The hearts were excised and the mRNA expression was evaluated by RT-qPCR using Taqman probe specific for each target gene; cyclophilin was used as a housekeeping gene. One and two-way ANOVA analysis were used to evaluate the time-of-day-dependent differential expression for each gene/group and their interactions. In general, the administration of T_3 promoted a marked alteration in the expression of Bmal1, Pdk4 and Ucp3, revealing a time-of-day-dependent responsiveness specially at the end of the dark period for Bmal1 and throughout the whole investigated period for Pdk4 and Ucp3. Our study shows that T_3 might acts as a Zeitgeber, and alters the cardiac functions, which may help to explain some metabolic and functional disorders observed in thyroid diseases.
Disclosure
This work was supported by CAPES and FAPESP (2013/05629-4).

DOI: 10.1530/endoabs.37.EP645

EP646

Influences on post-bariatric surgery satisfaction

Susana Garrido, Isabel Silva, Luisa Gonçalves, Ana Rita Caldas & M Helena Cardoso
S. de Endocrinologia, Diabetes e Metabolismo, Centro Hospitalar do Porto, Porto, Portugal.

Introduction
Post-bariatric surgery satisfaction relies on psychosocial and clinical factors. A questionnaire that evaluates this variable has recently been created and validated by the authors (Post-Bariatric Surgery Satisfaction Questionnaire).
Objective
To assess the relationship between treatment satisfaction and several demographic and clinical variables.
Methods
Patients submitted to bariatric surgery who presented to our Obesity Outpatient Clinic between June 2013 and December 2013 were asked to complete the Post-Bariatric Surgery Satisfaction Questionnaire (22 items, five-point scale – 1, very dissatisfied and 5, very satisfied). Demographic and clinical data were also collected.
Results
A total of 86 patients were included (67% submitted to laparoscopic gastric bypass and 33% to adjustable gastric banding): 86% females, median age 50 years (min–max = 23–73), median follow-up time since surgery 37 months (min–max = 1–220). Age, adjusted to percentage of excess BMI lost, was negatively correlated with 'physical well-being' ($r = -0.27$; $P = 0.012$) and with 'enhancement of movement capabilities' ($r = -0.25$; $P = 0.019$), but not with global satisfaction. There was no correlation between the degree of satisfaction and the follow-up time since surgery, nor differences between genders. There was a positive correlation between percentage of excess BMI lost and 15 of the items ($r = 0.21$–0.54; $P < 0.001$–0.047) and with global satisfaction ($r = 0.45$, $P < 0.001$). Patients submitted to adjustable gastric banding were less satisfied globally ($P = 0.007$) and in seven of the items. Results from the linear regression analysis indicate that the percentage of excess BMI lost and the type of surgery explain 29% of the variance in patients' global satisfaction. Both variables were statistically significant, with percentage of excess BMI lost recording a higher β value (0.45 and 0.20 respectively).
Conclusion
The percentage of excess BMI lost, the type of surgery, and patient's age influenced post-bariatric surgery satisfaction. However, these only partially explain treatment satisfaction. Other factors, namely psychosocial, are probably also involved.

DOI: 10.1530/endoabs.37.EP646

EP647

Effects of an 8-week supervised, structured lifestyle modification programme on anthropometric, metabolic, and cardiovascular risk factors in severely obese adults

Catherine Crowe[1], Irene Gibson[2], Katie Cunningham[1,2], Claire Kerins[2], Caroline Costello[2], Jane Windle[2], Paula O'Shea[3], Mary Hynes[1,4], Brian McGuire[1,4], Katriona Kilkelly[1], Helena Griffin[1], Timothy O'Brien[1], Jenni Jones[2,5] & Francis Finucane[1,5]
[1]Bariatric Medicine Service, Galway Diabetes Research Centre, HRB Clinical Research Facility, Galway, Ireland; [2]Croi, The West of Ireland Cardiac Foundation, Heart and Stroke Centre, Moyola Lane, Newcastle, Galway, Ireland; [3]Department of Clinical Biochemistry, Galway University Hospitals, Galway, Ireland; [4]School of Psychology, National University of Ireland, Galway, Ireland; [5]Discipline of Health Promotion, National Institute of Preventive Cardiology, National University of Ireland, Galway, Ireland.

Background
Lifestyle modification is fundamental to obesity treatment, but few studies have described the effects of structured lifestyle programmes specifically in bariatric patients. We sought to describe changes in anthropometric and metabolic characteristics in a cohort of bariatric patients after participation in a nurse-led, structured lifestyle programme.
Methods
We conducted a retrospective, observational cohort study of adults with a BMI $\geqq$40 kg/m^2 (or $\geqq$35 kg/m^2 with significant co-morbidity) who were attending a regional bariatric service and who completed a single centre, 8-week, nurse-led multidisciplinary lifestyle modification programme. Weight, height, waist circumference, blood pressure, HbA1c, fasting glucose and lipid profiles, functional capacity (Incremental Shuttle Walk Test) and anxiety, and depression scores before and after the programme were compared in per-protocol analyses.
Results
Of 183 bariatric patients enrolled, 150 (81.9%) completed the programme. Mean age of completers was 47.9$\pm$11.2 years. 34.7% were males. There were statistically significant reductions in weight (129.6$\pm$25.9 kg vs 126.9$\pm$26.1 kg, $P<0.001$), BMI (46.3$\pm$8.3 kg/m^2 vs 44.9$\pm$9.0 kg/m^2, $P<0.001$), waist circumference (133.0$\pm$17.1 cm vs 129.3$\pm$17.5 cm in women and 143.8$\pm$19.0 cm vs 135.1$\pm$17.9 cm in men, both $P<0.001$) as well as anxiety and depression scores, total- and LDL-cholesterol and triglyceride levels, with an increase in functional capacity (5.9$\pm$1.7 vs 6.8$\pm$2.1 METS, $P<0.001$) in completers at the end of the programme compared to the start. Blood pressure improved, with reductions in systolic and diastolic blood pressure from 135$\pm$16.2 to 131.6$\pm$17.1 ($P=0.009$) and 84.7$\pm$10.2 to 81.4$\pm$10.9 mmHg ($P<0.001$) respectively. The proportion of patients achieving target blood pressure increased from 50.3 to 59.3% ($P=0.04$). The proportion of patients with diabetes achieving HbA1c $<$53 mmol/mol increased from 28.6 to 42.9%, $P=0.02$.
Conclusions
Bariatric patients completing an eight week, nurse-led structured lifestyle programme had improved adiposity, fitness, lipid profiles, psychosocial health, blood pressure, and glycaemia. Further assessment of this programme in a pragmatic randomised controlled trial seems warranted.
Disclosure
The work was supported by a project grant from the Health Service Executive, Ireland.
DOI: 10.1530/endoabs.37.EP647

EP648

Skin tags and metabolic phenotype in severely obese adults: the STAMP cohort study

Catherine Crowe[1], Irene Gibson[2], Helena Griffin[1], Anette Murphy[3] & Francis Finucane[1]
[1]Bariatric Medicine Service, Galway Diabetes Research Centre, HRB Clinical Research Facility, Galway, Ireland; [2]Croí, The West of Ireland Cardiac Foundation, Galway, Ireland; [3]Department of Dermatology, Galway University Hospitals, Galway, Ireland.

Introduction
Skin tags (acrochordons) are a recognised feature of insulin resistance, but the extent to which they predict an adverse metabolic profile or the response to lifestyle modification in severely obese adults is not known.
Aims
We sought to quantify prospectively differences in anthropometric and metabolic characteristics in severely obese adults with acrochordons vs those without acrochordons, and to determine whether the presence of acrochordons predicted how well bariatric patients respond to an 8-week structured lifestyle programme.
Methods
Weight, height, blood pressure, fasting glucose, and lipid profiles and a detailed dermatological assessment were conducted in a cohort of bariatric patients undergoing a structured lifestyle modification programme. Baseline differences between those with and without acrochordons were measured using a two-sample *t*-test, while differences in the response to the lifestyle intervention were quantified using linear regression.
Results
100 bariatric patients (mean age 50$\pm$11.4 years, 31% males) were enrolled. There was a non-significant trend to those with acrochordons being heavier (weight 131.2$\pm$26.6 kg vs 121.8$\pm$15.3 kg, $P=0.06$) but also taller, with lower BMI (46.1$\pm$7.8 kg/m^2 vs 47.3$\pm$6.4 kg/m^2, $P=0.53$). They had higher HbA1c and systolic blood pressure (137.6$\pm$15.5 mmHg vs 124.4$\pm$9.1 mmHg, $P<0.001$), as expected. The intervention led to improvements in fitness and adiposity overall, but these improvements were no different in those with compared to those without acrochordons.
Discussion
In severely obese adults, acrochordons are an important marker of metabolic adversity but do not seem to predict the response to a lifestyle modification-programme.
Disclosure
This project was funded by Diabetes Care West, the Diabetes Charity for the West of Ireland.
DOI: 10.1530/endoabs.37.EP648

EP649

Prevalence of metabolic syndrome among human immunodeficiency virus and hepatitis C subjects in Southern Brazil

Maristela Beck, Helen Cezimbra Cezimbra, Fábio Pedro Pedro, Francisco Galarreta & Luiz Felipe Barin
Federal University of Santa Maria, Santa Maria, Brazil.

Objective
To investigate the metabolic syndrome and dyslipidemia prevalence among human immunodeficiency virus (HIV) and hepatitis C (HCV) subjects in Southern Brazil.
Methods
Cross-sectional study, including 127 subjects ($n=59$ HIV positive only, $n=36$ HIV/HCV positive, and $n=32$ HCV positive only) were accessed for HOMA index, metabolic syndrome, and dyslipidaemias.
Results
In HIV group there were 27% metabolic syndrome by IDF criteria and 26% by HOMA2-IR index (1.4 cut-off), 63% larger waist by IDF criteria and 26% abdominal obesity. To HIV/HCV coinfection group there were 30% metabolic syndrome by IDF, but 54% by HOMA2-IR index, 42% larger waist, but 52% abdominal obesity. To HCV group there were 25% metabolic syndrome by IDF and 38% by HOMA2-IR index, 67% larger waist, and 47% abdominal obesity.
Conclusions
The presence of HCV coinfection is responsible for alarming levels of insulin resistance, associated with a more favorable lipid profile that could act as a confounder in the clinical diagnosis of metabolic syndrome.
DOI: 10.1530/endoabs.37.EP649

Pituitary: basic and neuroendocrinology

EP650

Vadim Krylov[1,2], Ekaterina Dobreva[1], Nikolay Kuznetsov[1], Eugenia Marova[1], Leonid Ippolitov[2] & Nona Latkina[1]
[1]Endocrinology Research Center, Moscow, Russia; [2]First Moscow State Medical University, Moscow, Russia.

Introduction
Ectopic ACTH syndrome (EAS) is a rare cause of ACTH-dependent endogenous hypercortisolism.
Objective
The objective of this study was to analyse the clinical, biochemical, and radiological features, management, and treatment outcome of patients with EAS.

Design
It was a retrospective case-record study of 52 patients with EAS.
Materials and methods
Clinical, biochemical, and radiological features and response to therapy and survival were measured.
Results
The median follow-up was 7 years (range, 1–13 years). None of the dynamic tests achieved 100% accuracy. Imaging correctly identified the lesion at first investigation in 83% of cases. Bronchial carcinoid tumors were the most common cause of EAS ($n=34$; 65.4%), followed by other neuroendocrine tumors ($n=13$, 25%). In 9.6% (5) of patients, the source of EAS was never found. Octreotide scintigraphy and whole-body venous sampling were of limited value. Surgical attempt at curative resection was successful in 83% (43 of 52) of all patients; 9 (19.1%) responded generally well to bilateral adrenalectomy by vital necessity. Tumour histology and the presence of distant metastases were the main predictors of overall survival ($P<0.05$).
Conclusions
No single test provides to find the source of EAS correctly. Despite a variety of tests and imaging studies for the correct diagnosis of the EAS, up to 10% of cases present an occult EAS. These cases require a prolonged follow-up, review, and repetition of diagnostic tests and scans, but, if it is necessary, do bilateral adrenalectomy.

DOI: 10.1530/endoabs.37.EP650

EP651

Assessment of GH–IGF1 axis in adults with beta-thalassemia major: when to do a GH stimulation test?

Vincenzo De Sanctis[1], Ashraf Soliman[2], Giancarlo Candini[3] & Heba Elsedfy[4]
[1]Quisisana Hospital, Ferrara, Italy; [2]Hamad Medical Center, Doha, Qatar; [3]St. Anna Hospital, Ferrara, Italy; [4]Ain Shams University, Cairo, Egypt.

GHD in adults (AGHD) is a clinical syndrome associated with lack of positive well-being, depressed mood, feelings of social isolation, decreased energy, alterations in body composition with reduced bone and muscle mass, diminished exercise performance, and cardiac capacity. These manifestations are also common in adults with beta-thalassemia major (BTM). Performing provocative testing in all patients is cumbersome and expensive. Many studies suggested that IGF1 may be used for primary screening, to avoid performing GH stimulation tests in the majority of healthy or diseased subjects, when appropriate normative sex and age-correlated ranges are available.
Objectives
The International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescence Medicine (ICET-A) promoted a study to collect more information on IGF1 values in young adult Italian BTM patients.
Methods
Plasma total IGF1 was measured by CLIA method for 120 patients with BTM (58M, 62F) with an age range of 26.0–53.2 years for females and 20.8–51.2 years for males. 64.4% of the patients were above 35 years of age. The mean BMI was 22.48 ± 3.34 kg/m^2.
Results
IGF1 data, expressed in percentiles. No significant differences were observed between IGF1 values in men and women with TM.
Analysis and discussion
On the basis of the present results and data from the literature, ICET-A concluded their survey with the following recommendations: a GH stimulation test should be indicated in presence of the following clinical and laboratory parameters: short stature (HtSDS < -2.5), severe and/or prolonged iron overload, presence of severe osteoporosis and/or serum IGF1 level < -2 SDS. In adult TM patients, with normal liver function, an IGF1 level $<$50th percentile should be taken in consideration as a cut-off level for the GH assessment.

DOI: 10.1530/endoabs.37.EP651

EP652

IGF1 deficiency in newly diagnosed Graves' disease patients

Sorina Martin[1,2], Minodora Betivoiu[1], Suzana Florea[3] & Simona Fica[1,2]
[1]Endocrinology Department, Elias Hospital, Bucharest, Romania; [2]Endocrinology Department, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; [3]Laboratory Department, Elias Hospital, Bucharest, Romania.

Introduction
Thyroid hormones influence GH/IGF1 axis, but previous studies reported discrepant results regarding serum IGF1 levels in hyperthyroidism. We have therefore investigated, at diagnosis, the relationship between serum IGF1 levels/IGF1 z scores and clinical and biological characteristics of Graves' disease (GD) patients. We also compared IGF1 levels/IGF1 z scores, at diagnosis, between GD and autonomous hyperthyroidism patients.
Methods
This cross-sectional study included 119 newly diagnosed hyperthyroid patients (98 with GD and 21 with toxic multinodular goitre) that presented consecutively to our clinic. The main measured parameters: TSH, FT_4, FT_3, TT_3, thyroglobulin, TPOAb, ATA, TRAb, and IGF1. Patients were considered IGF-deficient if IGF1 z score was ≤ -2 S.D. from mean for age.
Results
In GD patients men had higher IGF1 levels ($P=0.023$) and IGF1 z scores ($P=0.013$) than women. 18.4% of GD patients were, at diagnosis, IGF1 deficient. Compared with patients without IGF1 deficiency, these patients presented, at diagnosis, higher thyroglobulin (median = 72.55, IQR = 116.02 vs median = 11.40, IQR = 80.74 ng/ml, $P=0.002$), FT_3 (median = 11.30, IQR = 7.64 vs median = 7.33, IQR = 5.72 pg/ml, $P=0.027$), and lower ATA (median = 20, IQR = 0 vs median = 34.05, IQR = 161 UI/ml, $P=0.001$) levels. Thyroglobulin was identified as strong predictor for IGF1 deficiency (AUROC = 0.732, 95% CI: 0.620–0.844, $P=0.002$; cut-off for thyroglobulin = 50.40 ng/ml, Se = 77.8%, Sp = 70%). IGF1 status was not influenced by gender ($P=0.08$), current smoking ($P=0.55$), goitre size ($P=0.53$), opthalmopathy ($P=0.33$), TRAb ($P=0.23$), and TPOAb status ($P=0.36$). The prevalence of IGF1 deficiency was higher in GD patients compared to patients with toxic goitre (18% vs 0%, $\chi^2=4.54$, $P=0.033$).
Conclusions
Our study shows, for the first time, the presence of IGF1 deficiency in nearly one-fifth of newly diagnosed GD patients. IGF1 deficiency was associated with lower ATA titres, higher thyroglobulin levels and more severe FT_3 hyperthyroidism. The presence of active GO did not influence IGF1 status. GD patients had higher prevalence of IGF1 deficiency than patients with toxic multinodular goitre.

DOI: 10.1530/endoabs.37.EP652

EP653

The NAD- and NADP-dependent blood lymphocytes dehydrogenases level and their interaction with GH/IGF1 in active acromegaly

Margarita A Dudina[1,3], Sergey A Dogadin[1,3] & Andrey A Sacvhenko[2]
[1]Krasnoyarsk State Medical University named after Prof. V. F. Voino-Yasenetsky, Krasnoyarsk, Russia; [2]Siberian Division, Institute for Medical Problems of the North, Russian Academy of Medical Sciences, Krasnoyarsk, Russia; [3]Krasnoyarsk Regional Clinical Hospital, Krasnoyarsk, Russia.

Somatotropin (GH) and IGF1 realise their influence on the system of intracellular metabolism and a number of important biochemical lymphocytes reactions through the receptor apparatus. It is allows to use the peripheral blood lymphocytes as the investigations object of intracellular metabolism disorders in acromegaly.
Aim
To study the NAD- and NADP-dependent dehydrogenases activity in blood lymphocytes in active acromegaly patients.
Methods
The activity of NAD(P)-dependent dehydrogenases in blood lymphocytes was studied in a group of 88 patients (35 men and 53 women) with active acromegaly, mean age 51.0 ± 12.5 years. The NAD(P)-dependent dehydrogenases activity was determined by biochemiluminescence method. The concentrations of GH and IGF1 were measured by ELISA.
Results
Studying the activity of mitochondrial NAD(P)-dependent dehydrogenases found a decrease in all NAD-dependent oxidoreductase: NADIDH, NADGDH, and MDH ($P<0.01$), which allows to state the low level flow in the tricarboxylic acid cycle. In active acromegaly were revealed the decreasing activity of all studied oxidoreductases: glucose-6-phosphate dehydrogenase ($P<0.01$), NAD–lactate dehydrogenase (LDH) ($P<0.001$), NADH–LDH ($P<0.001$), NAD–malate dehydrogenase (MDH) ($P<0.001$), NADH–MDH ($P<0.001$), NADP–MDH ($P<0.001$), NAD–glutamate dehydrogenases (GDH) and NADH–GDH ($P<0.001$), NADP–GDH and NADPH–GDH ($P<0.001$), NAD–isocitrate dehydrogenases (IDH) and NADP–IDH ($P<0.01$ and $P<0.001$ respectively), and glutathione reductase ($P<0.001$). Our data observed that decreasing activity of NADP–GDH positively correlated with the basal GH level ($r=+0.23$,

$P=0.04$) and NADP–MDH activity with IGF1 level ($r=+0.30$, $P=0.008$). The low NADH–MDH activity negatively correlated to the basal GH concentration ($P=-0.23$, $P=0.04$).
Conclusion
The chronic excess of GH and IGF1 in acromegaly causes a significant depletion of metabolic lymphocytes reserves. The main indicators of functional lymphocytes impairment in acromegaly are: the reduction of intermediates formation for the reactions of macromolecular synthesis and aerobic processes, the low intensity of glycolysis, nitrogen metabolism and inhibition of glutathione complex activity.

DOI: 10.1530/endoabs.37.EP653

EP654

Symptoms and complaints of patients with Cushing's disease (CD) according to Moscow region database of patients with CD

Irina Komerdus[1], Alexander Dreval[1], Anastasia Murzina[1], Timur Britvin[1], Larisa Akulkina[2] & Olga Nechaeva[1]
[1]Moscow Regional Research Clinical Institute N.A. M.F. Vladimirsky, Moscow, Russia; [2]Moscow State University, Moscow, Russia.

Objective
To evaluate the frequency of symptoms of Cushing's disease (CD) at baseline and it dependence on different quantities.
Material and methods
Clinical and laboratory data of 44 patients with CD (40 females and four males, 37.9 ± 10.5 years old), duration of the disease 35.5 (22; 75) months.
Results
Complaints: i) >80% – fatigability, weight gain, apathy, and headache, ii) 40–50% – loss of libido, bruisability, muscle weakness, insomnia, and hair loss, iii) <40% – irritability, striae, back pain, memory loss, impaired wound healing, increased appetite, and acne. 6/15 (34.1%) patients with back pain had spinal fracture. One patient with spinal fracture had no back pain. Regular menstruation – in 5/40 (12.5%) women, 12 (30%) – menstrual irregularities, and 23 (57.5%) – amenorrhea. Clinical examination: arterial hypertension – in 100% (by BPM). More than 70% had facial plethora, overweight/obesity, dorsocervical fat pad, hirsutism (females), and leg edema. BMI at baseline – 33.7 (30.4; 38.4). Normal weight 7%, 16.3% – overweight, 76.7% – obese (34.9% – I grade). Median weight gain 13.0 (10.0; 26.2) kg, correlated with duration of the disease ($r^2=0.2$; $P=0.007$). Positive correlations were found between: i) midnight serum cortisol level and apathy, muscle weakness, hair loss, and waist to hip ratio ($r^2=0.35$, $P=0.005$; $r^2=0.3$, $P=0.009$; $r^2=0.2$, $P=0.04$; and $r^2=0.2$, $P=0.049$ respectively), ii) morning serum cortisol level with apathy and impaired wound healing ($r^2=0.1$, $P=0.04$ and $r^2=0.2$, $P=0.006$), iii) morning and midnight serum ACTH levels with increased appetite ($r^2=0.2$, $P=0.01$ and $r^2=0.3$, $P=0.01$ respectively), iv) midnight serum ACTH with fatigability ($r^2=0.2$, $P=0.03$), and v) UFC with supraclavicular fat pads ($r^2=0.15$, $P=0.04$) . Back pain and striae correlated with BMI ($r^2=0.1$, $P=0.04$ and $r^2=0.17$, $P=0.006$ respectively). Weight gain and acne had a positive correlation with duration of the disease ($r^2=0.2$, $P=0.007$ and $r^2=0.14$, $P=0.001$ respectively).
Conclusions
The most frequent symptoms of CD are nonspecific. The strongest correlation observed between symptoms and midnight serum cortisol and ACTH levels.

DOI: 10.1530/endoabs.37.EP654

EP655

Transgenic human gene reporter cell line for evaluating interactions between androgen receptor and xenobiotics

Iveta Bartonkova, Aneta Novotna & Zdenek Dvorak
Department of Cell Biology and Genetics, Faculty of Science, Palacky University Olomouc, Olomouc, Czech Republic.

Androgen receptor (AR, NR3C4) is a 110-kDa ligand-activated transcriptional factor that belongs to the steroid hormone receptor superfamily. It has broad developmental effects and its mutations may have a great impact on pubertal development, genesis of prostatic hyperplasia, and even prostate cancer. Commonly known endogenous ligands of AR are testosterone and 5α-dihydrotestosterone (DHT). In the last years, several drugs and environmental pollutants were identified to alter AR activity leading to drug interactions or to endocrine disruption. Therefore, development of *in-vitro* experimental tools for analysing androgenic or antiandrogenic effects of various compounds is of great importance. In our work, we describe construction and characterisation of a novel stably transfected human reporter cell line AIZ-AR for assessment of transcriptional activity of human androgen receptor. Cell line AIZ-AR is derived from human prostate carcinoma epithelial cell line 22Rv1 that was stably transfected with a reporter plasmid containing three copies of androgen response regions (ARRs) followed by a single copy of androgen response element (ARE) from the promoter region of human prostate specific antigen (PSA) gene. Presented AIZ-AR cell line remained fully functional for over 60 days and more than 25 passages in the culture as well as after cryopreservation. Time-course analyses revealed that AIZ-AR cells allow detection of AR ligands as soon as after 8 h of the treatment. Upon dose–response analyses with 23 steroids in 96-well plate format, we observed induction of luciferase activity by androgens, but not by mineralocorticoids and oestrogens. Some glucocorticoids and progesterone also activated AR, but with potencies two to three orders of magnitude lower as compared with androgens. Taken together, we have developed a rapid, sensitive, selective, high-throughput and reproducible tool for detection of human AR ligands, with potential use in pharmacological and environmental applications.

DOI: 10.1530/endoabs.37.EP655

EP656

Diabetes insipidus as a rare neuroendocrine complication associated with Behcet's syndrome

Pooja Rao[1,2] & Maya Petlsverger[1,2]
[1]New Hanover Regional Medical Center, Wilmington, North Carolina, USA; [2]University of North Carolina, Chapel Hill, North Carolina, USA.

Behcet's disease (BD) is a chronic disease characterised by systemic involvement of blood vessels of all sizes on both arterial and venous circulation resulting in recurrent ulcers. The posterior infundibulo-hypophysitis, causing DI, has been commonly reported in association with systemic inflammatory/autoimmune disorders, however there are a handful of cases presenting with DI and Behcet's disease.
A 26-year-old African-American woman diagnosed with BD in 2006 after receiving a flu vaccine resulting in oral and genital ulcerations. She presented to ED with malaise, dizziness, severe polyuria, polydipsia with requests for iced water. On physical examination there was evidence of multiple oral apthous ulcers and genital ulcers. The serum level of sodium was 150 mEq/l, urine specific gravity was 1.003, and urine osmolality was 126 mOsm/kg. Estimated urine output volume was 5600 ml collected over 12 h. Complete evaluation of anterior pituitary hormone function tests including serum TSH, FT_4, FSH, LH, oestradiol, prolactin, IGF1, and ACTH stimulation test were unremarkable. MRI of the brain was suggestive of possible thickening of the pituitary stalk, but otherwise normal. Patient was started on oral DDAVP 0.1 mg twice daily with complete resolution of symptoms associated with DI. Formal water deprivation test was scheduled but not done due to a sudden resolution of DI over the course of 6 weeks.
Involvement of the CNS in Bechet's can be severe, leading to a devastating neurological deficit. Central DI in patients with BD has been rarely reported with possible correlation to autoimmune mediated vasculitis involving the blood vessels supplying the hypothalamus. In contrast with all prior cases reported, our patient's central DI had self-limiting course with complete resolution of symptoms (Molloy). Lymphocytic or autoimmune hypophysitis is commonly described as a transient but possibly relapsing condition.

DOI: 10.1530/endoabs.37.EP656

EP657

Effect of phenols and phthalates on rat and human pituitary cell proliferation

Laura Tapella[1], Antonella Sesta[2], Marco Losa[3], Francesco Cavagnini[2] & Francesca Pecori Giraldi[1,2]
[1]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; [2]Neuroendocrinology Research Laboratory, Istituto Auxologico Italiano, Milan, Italy; [3]Department of Neurosurgery, Ospedale San Raffaele, Milan, Italy.

An increased prevalence of acromegaly and pituitary tumors has recently been observed in high industrial density areas (Cannavò *et al*. *J Endocrinol* 2010) or after dioxin exposure (Pesatori *et al*. *Eur J Endocrinol* 2008). These data as well as *vitro* studies on endocrine disruptors (EDs) suggest that environmental pollutants may affect hormonal secretion and pituitary cell proliferation (Blake *et al*. *Proc Soc Exp Biol Med* 1997, Wilson *et al*. *Endocrinology* 1998, Maruyama *et al*. *Endocr J* 1999, Elango *et al*. *Gen Comp Endocrinol* 2006, Dang *et al*. *Toxicol Sci* 2007, Dang *et al*. *J Reprod Dev* 2009, Dang *et al*. *Steroids* 2009). The aim of our study was to verify the effect of endocrine disruptors on rat pituitary and human pituitary adenoma proliferative activity.

Methods

Pituitary primary cultures were incubated with 250 pM–1.25 nM phenol or *bis*-(2-ethylhexyl)-phthalate for 24 and 96 h. Cell viability, apoptosis and proliferation were assessed by ATP lite (Perkin Elmer, USA), MTT assay (Sigma), Caspases 3–7 (Promega), and 5-bromo-2′-deoxyuridine labeling (BrdU-labeling; Roche).

Results

In rat pituitary primary cultures, ATP cell content was reduced by phenol ($100 \pm 2\%$ vs $75.3 \pm 3.4\%$, $P < 0.0001$ control vs treatment) and *bis*-(2-ethylhexyl)-phthalate ($100 \pm 2\%$ vs $83.2 \pm 3.1\%$, $P < 0.0001$) at 24 h. After 96 h, ATP was clearly increased by phenol ($100 \pm 2\%$ vs $123.9 \pm 7\%$, $P < 0.05$, control vs treatment), less by *bis*-(2-ethylhexyl)-phthalate ($100 \pm 2\%$ vs $111.4 \pm 13\%$, NS). BrdU-labeling and MTT were also increased at the latter timepoint (BrdU-labeling: $100 \pm 12\%$ vs $136 \pm 12\%$, $P < 0.05$ and $100 \pm 12\%$ vs $137 \pm 8\%$, $P < 0.05$, for phenol and *bis*-(2-ethylhexyl)-phthalate respectively; MTT: $100 \pm 4\%$ vs $118 \pm 5\%$, $P < 0.05$ and $100 \pm 4\%$ vs $123 \pm 10\%$, $P < 0.05$, for phenol and *bis*-(2-ethylhexyl)-phthalate respectively). No changes in caspase activation were observed at 24 or 96 h. In two human GH-secreting primary adenomas, ATP content was increased by 40 and 100%, respectively, after 24 h incubation with 650 pM phenol.

Conclusions

Our findings show than phenol and *bis*-(2-ethylhexyl)-phthalate initially reduce then increase pituitary cell energy content; further, long-term incubation with EDs is associated with increased cell proliferation. This study indicates that both normal and adenomatous pituitary cell proliferation is modulated by endocrine disruptors, thus supporting the role of pollutants in pituitary adenoma aetiology.

Disclosure

This study was funded by the Italian Ministry for Teaching, University and Research (PRIN 2010–2011 #2010TYCL9B_004).

DOI: 10.1530/endoabs.37.EP657

EP658

Neuronal and synaptic ultra-structural organization in layer 5 of the human Gyrus temporalis

Rachida Yakoubi[1], Rachid Mosbah[1,2], Astrid Rollenhagen[3] & Joachim Lübke[3]

[1]Department of Biology, Faculty of sciences, University of Boumerdes, Boumerdes, Algeria; [2]Laboratory of Animal Eco-Biology, ENS, Kouba, Algeria; [3]Institute of Neuroscience and Medicine (INM-2), Jülich GmbH, Jülich, Germany.

Synapses are the key elements for signal transduction and plasticity in the brain. Despite a relatively large number of assumptions that have been made on the structure of mature cortical synapses in many other animal species, little is known about these structures in human. Hence, synapses in cortical layer 5 (L5), the main recipient layer of thalamocortical efferents, which representing the first station of cortical information processing were investigated structurally and quantitatively using serial ultrathin sections and digital electron microscopic images (DEMI) followed by three dimensional (3D) reconstruction and immunohistochemistry against glutamine synthetase. The quantitative 3D-reconstructions of cortical synapses will allow to directly comparing structural and functional aspects of synaptic transmission and plasticity thus leading to a better understanding of the function of cortical networks in the human neocortex.

The structural parameters such as the size, number, and distribution of active zones as well as the size and organisation of the pools of synaptic vesicles were the most critical factors investigated not only for the induction but also for the maintenance of synaptic transmission and plasticity in the neocortex. The DEMI examination followed by 3D-reconstruction of cortical L5 showed clearly a large pyramidal neurons (85%); GABAergic interneurons and astrocytes, multiple innervations on either the same or different dendrites, multivesicular bodies (MVBs) and mitochondria (two to eight) in the pre-synaptic element and perforations exist in the pre and post-synaptic densities. Besides, in 85% of the spines have a spine apparatus and a specialized form of endoplasmic reticulum. For the quantitative geometry study, the results showed a total pool of synaptic vesicles of 1671.57 ± 391.55 (ranging from 88 to 5841) with a mean diameter of 31.99 ± 0.87 nm, and a dense-core vesicles of 66.2 ± 11.27 nm, while, the volume of mitochondria and synaptic boutons and their surface were 0.05 ± 0.01 μm^3, 0.63 ± 0.09 μm^3, and 8.05 ± 0.27 μm^2 respectively. We can conclude that the morphological parameters observed in this study will help to better understand the mechanisms underlying synaptic transmission and plasticity in the adult cortical synapses.

DOI: 10.1530/endoabs.37.EP658

EP659

Influence of neurotransmitters on GnRH release in letrozole induced PCOS rat model

Nirja Chaudhari & Laxmipriya Nampoothiri

Department of Biochemistry, The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, India.

Background

Polycystic ovarian syndrome (PCOS) is a common reproductive-endocrine disorder seen in women; characterized by increased GnRH pulsatility, hyperandrogenism, and cyst formation in ovary. GnRH release is controlled by higher centres of brain namely, hypothalamus and pituitary through various feedback mechanisms, one of them being neurotransmitters. However, no clear data is available with respect to GnRH regulation by neurotransmitters in PCOS. The aim of the present study was to evaluate status of neurotransmitters and their receptors in PCOS and to correlate this with GnRH pulsatility.

Materials and methods

PCOS was induced in rats using letrozole – an aromatase inhibitor – and validated for structural and metabolic characteristics of PCOS. Neurotransmitters were estimated from different regions of rat brain by HPLC and detected electrochemically. RNA was isolated from hypothalamus and pituitary using TRIzol reagent and cDNA was synthesized by first strand cDNA synthesis kit. This cDNA was further used for real-time expression studies of gonadotropins and neurotransmitter receptors.

Results

PCOS rats demonstrated increased hypothalamic GnRH1; pituitary GnRHR and LHβ mRNA levels as compared to control rats. Reduced levels of norepinephrine, dopamine, serotonin, γ-amino butyric acid, and epinephrine with increased glutamate levels were observed in pituitary and hypothalamus of PCOS rats as compared to control rats. Expression of neurotransmitter receptors – 5HT1A, GABAB1, D2R, and α1A receptor decreased while that of NMDA receptor increased in hypothalamus and pituitary of PCOS rats.

Conclusion

Letrozole treated rat demonstrated hormonal and metabolic characteristics of PCOS with peripheral cysts in the ovary. Present study confirms that modulation in GnRH stimulatory as well as inhibitory neurotransmitters could have contributed to increased GnRH pulsatility, further resulting into increased LH to FSH ratio in PCOS.

DOI: 10.1530/endoabs.37.EP659

EP660

High metabolic risk is associated with small hypothalamic volume in acute lymphoblastic leukemia survivors 34 years after cranial radiotherapy

Cecilia Follin[1], Sanaz Gabery[2], Åsa Petrsen[2], Pia Maly Sundgren[1], Isabella Björkman-Burtcher[1], Peter Mannfolk[1], Jimmy Lätt[1] & Eva Marie Erfurth[1]

[1]Institution of Clinical Sciences, Lund University, Lund, Sweden; [2]Institution of Translational Neuroendocrinology, Lund, Sweden.

Background

Metabolic complications (obesity, lipid abnormalities, and insulin resistance) are prevalent in acute lymphoblastic leukemia (ALL) survivors treated with cranial radiotherapy (CRT). The hypothalamus (HT) is a complex area involved in endocrine function and metabolic control. In ALL survivors, assessment of the volume of the HT in relation to metabolic parameters including ghrelin, a peptide stimulating food intake, has not been performed previously.

Method
Thirty-four (21 women) ALL survivors, on complete hormone supplementation, were investigated 34 years after ALL diagnosis. Their median age was 38 (27–46) years and they had been treated with a CRT dose of 24 Gy. Comparison was made with 31 matched controls. Assessments of BMI (kg/m^2), waist (cm), fat mass (DEXA/kg), fat free mass (kg), plasma (p)-glucose (mmol/l), p-insulin (mIE/l), HOMA-index, s-leptin (μg/l), and s-ghrelin (ng/l) was performed. Magnetic resonance imaging (MRI) was performed to conduct volumetric analysis of the HT.
Results
S-leptin levels ($r=-0.4$, $P=0.04$) and fat mass ($r=-0.4$, $P=0.01$) were negatively correlated with the HT volume among the 34 ALL survivors, but not among the matched controls ($P>0.3$). There was a trend of a smaller HT volume among the ALL women compared to gender matched controls (846 mm^3 vs 869 mm^3, $P=0.06$). Significantly higher BMI (27.9 kg/m^2 vs 22.6 kg/m^2), waist (89 cm vs 79 cm), fat mass (29.9 kg vs 22.4 kg), p-insulin (10 mIE/l vs 6 mIE/l), HOMA-index (0.15 vs 0.07), leptin/kg fat mass (1.09 vs 0.6), and s-ghrelin (1560 ng/l vs 993 ng/l) and significantly lower fat free mass (35.4 kg vs 41.6 kg) were recorded among the female ALL survivors compared to matched controls (all $P<0.01$).
Conclusion
ALL women treated with CRT are at high risk of metabolic abnormalities in association with a smaller HT volume 34 years after ALL diagnosis. These findings suggest a hypothalamic effect of the metabolic complications.

DOI: 10.1530/endoabs.37.EP660

EP661

Long-term follow-up of cranially irradiated childhood leukaemia survivors show cognitive impairment and progressive decline in sustained attention, in spite of on complete hormone replacement

Cecilia Follin[1], Aki Johansson[2], Kai Österberg[2], Andrea Rovira[2], Magdalena Jansson[2], Thomas Wiebe[1] & Eva Marie Erfurth[1]
[1]Institution of Clinical Sciences, Lund University, Lund, Sweden; [2]Institution of Psychology, Lund University, Lund, Sweden.

Background
Survivors of childhood leukaemia (ALL) treated with cranial radiotherapy (CRT) are at risk for cognitive impairment. Whether the impairment progresses with follow-up time and if survivors with cognitive impairment have an increased risk for overweight, is unknown. We aimed to investigate the long-term cognitive functioning in ALL survivors treated with CRT in comparison to matched controls.
Method
Cognitive functioning was investigated in 38 ALL survivors, treated with CRT (24 Gy), at a median age of 5 years (1–17). The survivors were on complete hormone substitution. Median age at follow-up was 38 years (33–46) and the survivors were investigated 34 years (26–40) after diagnosis. Comparisons were made with 28 controls, matched for gender and age.
Results
After 34 years of treatment survivors demonstrated a lower performance in vocabulary, memory, learning capacity, spatial ability, executive functions, and attention (all, $P<0.001$), compared to controls. 58t % of the survivors had moderate/severe impairment in visuo-spatial function and episodic memory, and had significantly higher BMI (28.4 vs 25.9) ($P=0.01$), compared to survivors with normal cognitive function. Furthermore, this group was treated at younger age (3; 1–9) compared to the survivors with normal cognition (6; 3–17). From the age of 26 years to the age of 38 years, and in comparison to the same matched controls 69%, of the survivors, demonstrated a decline in psychomotor speed tests of reaction time (RT) (sustained attention) ($P=0.02$ and $P<0.001$). A significantly higher BMI was recorded among the survivors with an increased RT of >15%, compared to survivors with <15% increased RT.
Conclusion
34 years after ALL diagnosis, we report persistent cognitive impairment and a progressive decline in sustained attention in survivors. The survivors with overweight had the most attenuated impairment in cognitive function. Intervention strategies should be multidimensional and include tailored psychosocial and healthy life-style support.

DOI: 10.1530/endoabs.37.EP661

EP662

Neuroendocrine complications of radiation therapy for pituitary somatotropinomas

Zamira Khalimova[1] & Saodat Issaeva[1,2]
[1]Republican Specialized Scientific-Practical Medical Center of Endocrinology, Tashkent, Uzbekistan; [2]Tashkent Pediatric Medical Center, Tashkent, Uzbekistan.

The purpose of the study
To examine the incidence of neuroendocrine complications after radiation therapy (RT) of pituitary somatotropinomas.
Materials and methods
30 patients surveyed after receiving RT at a dose of 45 g in 25 fractions a day. Of these, 21 (70%) females, 9 (30%) men. The age of patients ranged from 36 to 71 years. 37% of them had pituitary macroadenoma with para-, supra-, and infrasellar growth. Duration of illness was 15 years on average. Period of observation after RT averaged to 10 years. The levels of GH, IGF1, PRL, TSH, LH, FSH, fT_4, cortisol, oestradiol, testosterone, CT/MRI of the brain covering pituitary, visual field and acuity tests, and fundoscopy were assessed. All patients received RT in combination with drug therapy. 6 (20%) received RT with drug therapy, 11 (37%) after TAG and 13 (43%) were primary. All parameters were checked before (I group) and a year or more after RT (II group).
Results
The following impairments took place in I group: increased GH ($M=107$), IGF1 ($M=1138$) in 75%, and PRL in 33%; decreased gonadotropins in 80%, TSH and fT_4 in 17%, cortisol in 10%, decreased visual acuity in 30%, menstrual disorder in 62%, and impaired potency in 11% of patients. Group II showed following results: GH ($M=33$) and IGF1 ($M=434$) in 38%, PRL in 9%; decreased gonadotropins in 80%, TSH and fT_4 in 30%, cortisol in 50%, menstrual disorder in 67%, impaired potency in 33%, and decreased visual acuity in 57% of patients. Moreover, 20% developed ESS and 3% necrosis of brain tissue.
Conclusions
RT in pituitary somatotropinomas leads to the stabilization of the pathological process.

DOI: 10.1530/endoabs.37.EP662

EP663

Social stress promotes changes in local metabolism of glucocorticoids

Jiri Pacha[1], Petra Klusonova[1], Peter Ergang[1], Martin Vodicka[1], Anna Mikulecka[1] & Petr Zach[2]
[1]Institute of Physiology, Czech Academy of Sciences, Prague, Czech Republic; [2]3rd Faculty of Medicine, Institute of Anatomy, Charles University, Prague, Czech Republic.

Stressful experiences produce profound physiological and behavioural disturbances that may contribute to many psychiatric disorders. Stress activates HPA axis whose end products glucocorticoids modulate immune cells and cytokine activity. Local effect of glucocorticoids depends not only on its concentration but also on the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11HSD1), which amplifies intracellular glucocorticoid concentration by the conversion of inactive 11-dehydrocorticosterone to active corticosterone. As cytokines are potent modulators of 11HSD1, it was interested to establish whether cytokines could modulate metabolism of glucocorticoids in response to various stressors. Fisher 344 rats were exposed to chronic emotional homotypic stress (resident-intruder paradigm) or short-term variable stress combining emotional and physical stressors. Plasma level of corticosterone, TNFα and IL1β were measured by commercial kits, expression of 11HSD1, TNFα, and IL1β mRNAs by RT-PCR and 11-reductase activity by radiometric assay. We found that long-term homotypic stress increased corticosterone and decreased TNFα and IL1β in plasma. Expression of 11HSD1 mRNA was increased in thymus and spleen but not in mesenteric lymph nodes and liver. Similar pattern was found in expression of TNFα and IL1β – both cytokines were upregulated in thymus and spleen but not in liver and lymph nodes. Stimulatory effect of stress on 11-redutase activity was observed in both mobile cells and stroma of all three lymphoid organs. Vagotomy did not affect the stress-dependent upregulation of 11HSD1 in spleen and mesenteric lymph nodes. In contrast to chronic stress, the short-term variable stress up-regulated 11HSD1 only in thymus but not in spleen and lymph nodes. The findings demonstrate that a powerful stressor may have strong effect on glucocorticoid signaling in some peripheral organs, in particular lymphoid, but the nature of the effect varies with the specificity of stress and tissue. In lymphoid organs, the stressful episodes increase 11HSD1 in parallel with upregulation of TNFα and IL1β, which have been shown previously to stimulate 11HSD1 in vitro.

Disclosure
This work was supported by the Czech Science Foundation (grant numbers 15-07268S and P303/10/0969).
DOI: 10.1530/endoabs.37.EP663

EP664

The status of blood antioxidant system in patients with active acromegaly

Maria Faassen[1], Maria Pankratova[1], Natalia Molitvoslovova[1], Valentina Peterkova[1], Adil Baizhumanov[2], Alexander Yusipovich[2], Svetlana Kovalenko[2] & Georgy Maksimov[2]
[1]Endocrinology Research Centre, Moscow, Russia; [2]Biophysics Department, Lomonosov Moscow State University, Moscow, Russia.

Introduction
The oxidative stress is supposed to be key factor in multiple diseases.
The aim of the study was to examine the effects of excessive GH secretion on the blood antioxidant system: total antioxidant capacity (TAC) of plasma; superoxide dismutase (SOD) and catalase activities (CAT); ceruloplasmin (CP); non-protein thiol (NT), and level of thiobarbituric acid reactive substances (TBARS).
Materials
Eleven patients with active acromegaly were included in the study. The state of the antioxidant system was examined and compared with these of a control group (nine persons).
Results
In patients with acromegaly the TAC levels and SOD activity were significantly lower (for 20 and 30%), than corresponding control data, whilst TBARS and CP levels were significantly higher (for 50 and 40% respectively).
Conclusions
The present work has demonstrated that parameters of the blood antioxidant system are impaired in patients with active acromegaly, what indicates the development of oxidative stress.
Disclosure
Authors have nothing to disclose.

DOI: 10.1530/endoabs.37.EP664

EP665

The PATRO adult study of Omnitrope® for the treatment of adult patients with GH deficiency: latest results

Paolo Beck-Peccoz[1], Charlotte Höybye[2], Robert D Murray[3], Suat Simsek[4], Alfonso Leal-Cerro[5], Markus Zabransky[6] & Gunter Stalla[7]
[1]Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; [2]Department of Endocrinology, Metabolism and Diabetology, Karolinska University Hospital, Stockholm, Sweden; [3]Department of Endocrinology, Leeds Centre for Diabetes and Endocrinology, St James's University Hospital, Leeds, UK; [4]Medisch Centrum Alkmaar, Alkmaar, The Netherlands; [5]Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío, Seville, Spain; [6]Sandoz International GmbH, Holzkirchen, Germany; [7]Department of Internal Medicine, Endocrinology and Clinical Chemistry, Max Planck Institute of Psychiatry, Munich, Germany.

Introduction
PATRO adults is an ongoing, international, open, longitudinal, non-interventional study of the long-term safety and efficacy of recombinant human GH (rhGH; Omnitrope, Sandoz). The study will provide further 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
Adults who are receiving treatment with Omnitrope and who have provided informed consent are eligible for inclusion. Patients treated with another rhGH before starting Omnitrope therapy can also be included. The primary objective of the study is to assess the safety and efficacy of Omnitrope in adults treated in routine clinical practice. Particular emphasis is placed on the risk of glucose intolerance or diabetes and normalisation of IGF1 levels.
Results
As of November 2014, 800 patients have been enrolled in the study; 414 (52%) have received previous GH treatment. Mean (S.D.) age of enrolled patients is 50.4 (15.5) years, and mean (S.D.) BMI is 29.7 (6.5) kg/m^2. So far, 1033 adverse events (AEs) have been reported in 321 (40%) patients, with 92 (8.9%, in 59 (7.4%) patients) regarded as serious. Eighty-nine AEs (8.6%) in 58 (7.3%) patients were suspected as drug-related. These included 17 nervous system disorders, 17 general disorders/administration site conditions, 11 musculoskeletal/connective tissue disorders, and 11 investigations (increased IGF levels). One serious AE (dyspnoea) in 1 (0.2%) patient was suspected as drug-related. Seventy-six patients have discontinued treatment; 17 of these did so due to an AE.
Conclusions
Based on this interim analysis, Omnitrope treatment in adults with GHD is well tolerated in real-life clinical practice, both in rhGH-naïve and previously treated patients. The PATRO adults study will continue to provide important data on the diabetogenic potential and overall safety of long-term GH treatment in this population.
Disclosure
The PATRO adults study is funded by Sandoz.

DOI: 10.1530/endoabs.37.EP665

EP666

Dose interval injection extension and costs of lanreotide Autogel 120 mg used in routine acromegaly care in Poland: 2 years data from Lanro study

Ewa Orlewska[1], Beata Kos-Kudla[2], Jerzy Sowinski[3], Krzysztof Sworczak[4] & Wojciech Zgliczynski[5]
[1]Faculty of Health Sciences, The Jan Kochanowski University, Kielce, Poland; [2]Division of Endocrinology, Department of Pathophysiology and Endocrinology, Silesian Medical University, Katowice, Poland; [3]Chair and Department of Endocrinology, Metabolism and Internal Diseases, Poznan University of Medical Sciences, Poznan, Poland; [4]Endocrinology and Internal Diseases Department, Medical University, Gdansk, Poland; [5]Centre of Postgraduate Medical Education, Warsaw, Poland.

Objective
To determine the percentage of patients with acromegaly who received lanreotide Autogel 120 mg (ATG120) in extended duration interval and to evaluate the mean costs of ATG120 administered as part of routine care in Poland.
Methods
National, multicentre, non-interventional, observational prospective study with 2-years' time horizon. The study population consisted of adult acromegaly patients who received at least three injections of ATG120 before inclusion. The endpoints were: percentage of patients treated with ATG120 at an extended duration interval (>4 weeks) and mean cost of ATG120. Costs were calculated in PLN from the public health-care payer and patient perspective for the year 2014 (one PLN$=0.25$ EURO).
Results
151 patients suffering from acromegaly for at least 1 year were screened and 143 enrolled in 35 centres. Of those, 11 patients were excluded from the analysis because of missing of follow-up visits or because they did not complete the treatment period. 70% of them were women, 81% had macroadenoma, and 75% underwent surgical treatment in the past. During 2 years, changes in the treatment pattern – decrease or increase of injection interval or change of treatment, were reported in 41 (31%) patients. In other patients treatment has not been changed. 63 patients (48%) received ATG120 at an extended duration interval. The mean number of days between injections was 35.1 (S.D. 8.2). ATG120 was predominantly administered in out-patient setting (84%) and by health-care professional (97%). The mean cost of ATG120 per patient per month was 4062.5 PLN and 3.6 PLN from the public payer and patient perspective respectively. Meanwhile the retail price of ATG120 per pack is 4770.5 PLN.
Conclusion
The results demonstrated that extended duration interval of ATG120 is used in almost half of acromegaly patients, indicating the reduction of financial burden for the health care system.
Disclosure
This study was founded by Ipsen Poland sp. z o.o.

DOI: 10.1530/endoabs.37.EP666

EP667

GH therapy has a beneficial effect on HbA1c levels in adult patients with GH deficiency: a report from the NordiNet® International Outcome Study

Matthias Weber[1], Birgitte Tønnes Pedersen[2], Effie Pournara[3], Jens Sandahl Christiansen[4] & Charlotte Höybye[5]
[1]I. Medical Clinic, University of Mainz, Mainz, Germany; [2]Novo Nordisk A/S, Søborg, Denmark; [3]Novo Nordisk Health Care AG, Zurich, Switzerland; [4]Aarhus University Hospital, Aarhus C, Denmark; [5]Karolinska University Hospital, Stockholm, Sweden.

Introduction
The clinical significance of the impact of GH on glucose homeostasis in adults with GH deficiency (GHD) remains unclear. We report the impact of 4 years of continuous GH therapy on HbA1c and progression to diabetes.
Methods
Data were analysed from patients with adult-onset GHD (>20 years old) enrolled in NordiNet® International Outcome Study (IOS) (NCT00960128), an observational study, and treated with GH (Norditropin®, Novo Nordisk A/S, Denmark) for 4 years. Change in HbA1c (ΔHbA1c) from baseline was calculated for all patients, by GH dose group (≤0.2 and >0.2 mg/day), for patients with clinically relevant decrease in HbA1c (≥0.3% decrease), unchanged, or clinically relevant increase in HbA1c (≥0.3% increase), and by baseline health status (% patients) (low–normal, HbA1c <5.8% (75.2%); pre-diabetes/high–normal, HbA1c 5.8–<6.5% (17.3%); diabetes, HbA1c ≥6.5% (7.5%)).
Results
Among the 278 patients (48% females) mean±S.D. age was 49.4±14.5 years, BMI, 29.0±6.1 kg/m^2 and HbA1c 5.29±0.85%. Patients receiving ≤0.2 mg/day GH (n=120) were older than those receiving >0.2 mg/day GH (53.9 years vs 46.0 years). At 4 years, 54.32% of patients had no change, 20.14% a decrease and 25.54% an increase in HbA1c. ΔHbA1c at 4 years was greater for patients receiving ≤0.2 than >0.2 mg/day GH (0.10±0.61% vs −0.20±0.56%). A significant association (P=0.045) between GH dose >0.2 mg/day and the proportion of patients with clinically significant decrease in HbA1c (≥0.3% vs baseline) was observed. After 4 years, among patients with pre-diabetes/high–normal HbA1c at baseline (n=48), 48% had low–normal HbA1c, 10% developed diabetes, and 42% were unchanged. No overall association between change in health status (baseline to 4 years) and GH dose was found.
Conclusions
Four years of GH therapy was not associated with deterioration in HbA1c or progression to diabetes. Indeed, almost half of patients with pre-diabetes/high–normal HbA1c showed a clinically relevant improvement in health status after 4 years of GH therapy.
Disclosure
This study was sponsored by Novo Nordisk Health Care AG.
DOI: 10.1530/endoabs.37.EP667

EP668

Radio-induced meningioma: a long-term consequence of pituitary radiotherapy

Concepción Páramo-Fernández, Yolanda López-Vázquez, Gloria Barragáns, Angel Martínez, Javier Lago & Susana Gomara
Complejo Hospitalario Universitario de Vigo, Vigo, Spain.

Long-term sequels of pituitary radiotherapy include hypopituitarism, optic nerve atrophy, sensorineural hearing loss, neurocognitive impairment and second intracranial neoplasms, the meningioma being the most frequent. The cumulative incidence of second cerebral tumours within 20 years of the radiation is 2% and, unlike its primary forms, they show a more aggressive atypical histology, and the age of appearance varies depending on the latency time, which in its turn is proportional to the dose of received radiation.
Material and methods
We present three patients with meningiomas secondary to pituitary adenoma radiation, all of them of somatomammotroph lineage. All these meningiomas were developed on the area of pituitary irradiation, over 20 years after it, and they were neither present on the diagnose nor was there an environmental or genetic proneoplastic condition.
Results
Case 1: A 65-year-old man, diagnosed with macroprolactinoma on 1977. He received cobalt therapy after a subtotal resection of the tumour. He debuted 29 years later with fronto-orbital cephalea in relation with a prebulbar meningioma with extension to the foramen magnum.
Case 2: A 72-year-old male diagnosed with GH releasing macroadenoma in 1968. He was treated with cobalt-therapy and 44 years later presented with apathy and bradypsychia. Neuroimaging revealed the presence of a right frontal convexity meningioma.
Case 3: A 50-year-old man, diagnosed with a macroprolactinoma on 1973 and treated with radiotherapy. After 40 years of treatment, a 1′1 cm meningioma is discovered on the right sylvian fissure following a study of dementia due to memory loss, mental dispersion, and depressed mood. The total dose of radiation received was 40–50 Gy on each patient.
Conclusions
Second cerebral neoplasms may appear more than 30 years after the pituitary radiotherapy and its detection advices permanent monitoring in neuroendocrinology consultations by means of periodic neuroimaging studies.
DOI: 10.1530/endoabs.37.EP668

EP669

MiR-7 has a role in behaviour of somatotroph adenomas

Ruth Sanchez-Ortiga[1], Laura Sanchez-Tejada[5], Cristina Lamas[2], Rosa Cámara[4], Javier Abarca[6], Irene Monjas[7], Pedro Riesgo[8], Carmen Fajardo[3] & Antonio Picó[1]
[1]Endocrinology Department, Hospital General Universitario Alicante, Alicante, Spain; [2]Endocrinology Department, Hospital General Universitario Albacete, Albacete, Spain; [3]Endocrinology Department, Hospital La Ribera, Alzira, Spain; [4]Endocrinology Department, Hospital Universitario La Fe, Valencia, Spain; [5]Research Unit, Hospital General Universitario Alicante, Alicante, Spain; [6]Neurosurgery Department, Hospital General Universitario Alicante, Alicante, Spain; [7]Otorhinolaryngology Department, Hospital General Universitario Alicante, Alicante, Spain; [8]Neurosurgery Department, Hospital La Ribera, Alzira, Spain.

Purpose
IGF receptor 1 (IGF1R) and epidermal growth factor receptor (EGFR) are receptors tyrosine-kinase (RTK) whose altered signaling are critical factors in development of many types of tumours. These RTK are some of the main targets of the microRNA miR-7. This important tumor supressor miRNA has the ability to inhibit the motility, invasiveness and anchorage-independent growth, suggesting a strong therapeutic potential in many types of cancer. Pituitary adenomas (PA) are a heterogeneous group of tumors with diverse clinical behaviour. The aim of this study is to investigate the role of this miRNA in the behaviour of different PA subtypes.
Methods
In this cross-sectional descriptive study, we evaluated miR-7 by qRT-PCR on 60 human PA: 29 gonadotrophs (GT), 15 somatotrophs (ST), eight functioning corticotroph (CT), and eight silent corticotroph adenomas (SCA). Nine healthy pituitary from autopsies were used as calibrator reference. Aggressiveness was graded according to invasiveness (Hardy's grade IV) and Ki-67 gene expression (>2.59-fold change (FC)).
Results
MiR-7 showed different expression depending on PA subtype (P=0.005). Its highest expression was found in ST (5.21 (2.06–5.80) FC), in which miR-7 was mainly overexpressed and only repressed in 33% of ST with high grade of aggressiveness. Thus, miR-7 repression entailed a risk of 7 (2–25) times higher to ST tumours reached high grade of aggressiveness (P=0.038). In addition, miR-7 was negatively correlated with age (r=−0.583, P=0.022). In GT and SCA, expression was similar (0.91 (0.46–4.70) and 0.80 (0.26–3.18) FC respectively) and in CT, miR-7 showed its lower expression (0.69 (0.31–1.32) FC). However, we did not find associations with their behaviours.
Conclusion
According with our results, miR-7 plays an important role in the behaviour on ST, acting as tumor supressor miRNA and participating against its aggressiveness. Further studies are needed to clarify its potential therapeutic utility.
Disclosure
This work was supported by FISABIO (FCVI-HGUA-2012-C01).
DOI: 10.1530/endoabs.37.EP669

EP670

The dynamics of anthropometric and hormonal parameters in adolescents (boys) with physical and sexual development during therapy with thyroid medications

Utkir Mavlonov[1,2], Yulduz Urmanova[1,2], Shakhlo Babakhodgaeva[1,2], Feruza Khodgaeva[1,2] & Nazira Rikhsieva[1,2]
[1]Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan; [2]Bukhara Endocrine Regional Clinic, Bukhara, Uzbekistan.

The purpose of research
To study the dynamics of anthropometric and hormonal indicators of adolescent boys with physical and sexual development (ZFPR) and iodine deficiency disorders (IDD), received treatment for 12 months replacement therapy of thyroid (jodomarin, L-thyroxine, Berlin-Chemie).
Material and methods
We have inspected and examined the whole for the period from 30th May 2012 to 15th October 2013 1066 adolescent boys in different regions of Uzbekistan. In the city of Bukhara and four districts of Bukhara region were examined 523 adolescents (boys) in Namangan region – 200, in Tashkent – 343, aged 11–17 years. The main contingent made up of college students and schools.
In the future, selected 163 patients with various disorders of growth and sexual development was carried spectrum of research includes the study of endocrine status, clinical, biochemical, and hormonal.
Among these patients, we have selected a further 60 adolescents with ZFPR (delayed puberty and growth) + IDD from the city of Bukhara and Bukhara region, which were carried out additional studies (TSH, T_4, X-ray hand, skull, EEG, Echo-EG, etc.) and anthropometric estimates the dynamics before and 12 months after replacement therapy with thyroid (jodomarin 100 and 150 mg/day, L-thyroxine 25 and 50 μg/day).
The results of the study
At 3, 6, and 12 months after treatment with thyroid dynamics in patients with mental retardation + IDD there was a significant improvement in hormonal parameters, namely, the mean values of TSH and free T_4 ($P<0.05$). If the growth rate in patients with CP + IDD before treatment was 5.3 ± 0.2 cm/year, after 12 months of treatment with thyroid averaged 6.3 ± 0.3 cm/year (6.6–9.6 cm/year), and absolute increase growth in 12 months in average: 8.1 ± 0.4 cm.
Conclusions
Thus, on the basis of completed research can be concluded that therapy with thyroid cancer in patients with mental retardation + IDD significantly improves both hormonal and anthropometric indicators, which confirms the need for primary prevention of IDD among children and adolescents.

DOI: 10.1530/endoabs.37.EP670

EP671

G protein signalling of native somatostatin receptors 2 and 5 in pituitary cells using a fluorescence-based membrane potential assay

Thomas Günther & Stefan Schulz
Institute of Pharmacology and Toxikology, Jena, Thuringia, Germany.

Somatostatin and dopamine receptors are the major G_i-coupled receptors in somatotrope cells that inhibit hormone secretion from the anterior pituitary. Here, we adapted a novel fluorescence-based screening assay to characterize somatostatin and dopamine receptor signaling in a time-resolved manner. This minimal-invasive technique provides a robust and reliable read out for ligand-induced receptor activation in permanent cell lines and primary pituitary culture. The pituitary cell line AtT-20 expresses both sst2 and sst5 endogenously. Exposure of WT AtT-20 cells to the sst2- and sst5-selective agonists BIM23120 and BIM23268, respectively, promoted a PTX- and tertiapin-Q-sensitive reduction in fluorescent signal intensity, which is indicative of activation of G protein-coupled inwardly rectifying potassium (GIRK) channels. In contrast, exposure to BIM23926 (sst1-selective), L-796/778 (sst3-selective), or L-803/067 (sst4-selective) did not produce any change in fluorescent signal intensity. However, after heterologous expression of sst1, sst3, or sst4 receptors BIM23926 and L-796/778 but not L-803/087 promoted a reduction in fluorescent signal indicating that sst1 and sst3 receptors can also couple to GIRK channels. Similar activation of GIRK channels by dopamine in AtT-20 required overexpression of D2 dopamine receptors.
Disclosure
German Research Foundation.

DOI: 10.1530/endoabs.37.EP671

EP672

The use of an oral salt load followed by furosemide in the treatment of euvolemic SIADH-induced hyponatremia

Ana Ortolá[1], Irene Crespo[1], Teresa Ruiz-Gracia[1], Emilia Gomez-Hoyos[2], Martin Cuesta[3], Rona Penso[1], Angela Amengual[1], Paz de Miguel[1], Alfonso Calle-Pascual[1] & Isabelle Runkle[1]
[1]Hospital Clinico San Carlos, Madrid, Spain; [2]Hospital Clinico de Valladoilid, Valladolid, Spain; [3]Beaumont Hospital, Dublin, Ireland.

Introduction
Furosemide can be used in the treatment of SIADH. However, to be effective, renal medulla osmolality (Osm_{RM}) as reflected in urinary osmolality (U_{OSM}) must be high. Sodium is the most important contributor to Osm_{RM}, which increases following the administration of oral salt. We analyze the use of an oral salt load followed by furosemide for the acute/short-term treatment of euvolemic SIADH hyponatremia.
Methods
Retrospective analysis of nine patients with SIADH-induced hyponatremia and moderate hyponatremic encephalopathy receiving 4–5 g of oral salt, followed 3 h later by 20 mg furosemide i.v. or 40 mg furosemide po (salt-plus-furosemide). Serum sodium levels (SNa), serum potassium (SK), and urinary sodium (UNa) were measured at baseline, and 12–16 h following salt administration. In six out of nine patients, a SNa level was available from 24 h or less previously (PSNa). Electrolytes in mmol/l. Plasma (P_{OSM}) and U_{OSM} in mOsm/kg. Wilcoxon and Mann–Whitney *U* tests. SPSS15.
Results
Baseline: 4/9 (44.4%) were women. Median age: 69.3 (S.D.: 20.7). Prior to salt-plus-furosemide, SNa levels were descending in five out of six patients with a median change of −1.5 (IQR −2.3 to −0.25). PSNa: 121 (S.D.: 4.5). Initial SNa: 119 (S.D.: 4.8), SK: 4.4 (S.D.: 0.6), UNa 54 (IQR: 42.5–86), P_{OSM} 249 (S.D.: 7.9), and U_{OSM} 449 (S.D.: 251.2). Following salt-plus-furosemide, SNa rose from 3 to 7 mmol/l, with a median increment of 5 (IQR: 4–7), reaching a SNa of 124 (IQR: 121–127), SK: 4.1 (S.D.: 0.4), UNa 66.4 (S.D.: 24.6), P_{OSM}: 259 (S.D.: 7.4), and U_{OSM}: 370 (S.D.: 151.4). The SNa change post salt-plus-furosemide vs the change prior to salt-plus-furosemide was statistically significant ($P=0.027$). SK descent was also significant ($P=0.017$). All blood pressure levels were below 130/85 mmHg before and after salt administration.
Conclusions
The oral administration of 4–5 g of salt followed by furosemide was useful for the acute/short-term treatment of euvolemic SIADH-hyponatremia in our patients. However, this therapy should not be attempted in severe hyponatremia, since a minimum 4 mmol/l SNa rise was not assured.

DOI: 10.1530/endoabs.37.EP672

EP673

Progressive reduction of tolvaptan doses in the treatment of chronic SIADH

Teresa Ruiz-Gracia[1], Ana Ortolá[1], Irene Crespo[1], Alejando Santiago[1], Emilia Gomez-Hoyos[2], Lourdes Recio[1], Martin Cuesta[3], Maria Paz Pacheco[1], Alfonso Calle-Pascual[1] & Isabelle Runkle[1]
[1]Hospital Clínico San Carlos, Madrid, Spain; [2]Hospital Clinico de Valladolid, Valladolid, Spain; [3]Beaumont Hospital, Dublin, Ireland.

Introduction
Chronic tolvaptan (TV) therapy has been found to be safe and effective in the treatment of chronic SIADH. However, experience with modification of doses over time is limited.
Methods
We conducted a retrospective analysis of weekly TV doses (mg) in 41 patients with chronic SIADH treated for a minimum of 3 months, seen a week following discharge and monthly thereafter. Serum sodium (SNa) goal was 137–140 mmol/l, with 50% TV dose reduction when SNa ≥ 141 and increase when SNa <137. SNa (mmol/l) corrected for glycemia/total proteins. Kruskal–Wallis, Mann–Whitney *U*, SPSS15.
Results
25/41(61%) women, median age of 76 (67–85). Median Nadir SNa: 119 (S.D.: 6.2). Etiology of SIADH: idiopathic 12/41 (29.3%), oncological 10/41 (24.4)%, pulmonary 7/41 (17.1%), pharmacological 5/41 (12.2%), neurological 5/41 (12.2%), and others 2/41 (4.9%). Average duration of therapy was 18.4 (S.D.: 12.0) months. Median weekly hospital discharge dose: 105 (105–105) with SNa 137 (S.D.: 3.0); at 1 month: 105 (78.7–105), SNa 139 (S.D.: 3.3); at 3 months: 52.5

(26.3–135), SNa 138 (s.d.: 3.7); at 6 months: 52.5 (25.3–88.1), SNa 139 (s.d.: 3.3); and at 1 year: 37.5 (22.5–105), SNa 138 (s.d.: 2.7). Oncological patients needed higher doses when compared to the rest at discharge: 157.5 (105–210) vs 105 (105–105), $P=0.049$; at 3 months: 210 (52.5–236.2) vs 52.5 (26.3–105), $P=0.021$; and at 6 months 105 (52.5–420) vs 52.5 (22.5–75), $P=0.022$. Pharmacological patients needed lower doses when compared to the rest at 3 months: 26.25 (18.8–65.6) vs 52.5 (52.5–198.8), $P=0.042$, at 6 months 22.5 (7.5–37.5) vs 52.5 (28.1–105), $P=0.010$, and at 1 year 22.5 (11.3–28.1) vs 52.5 (30–105), $P=0.024$. Side effects: 1/41 patients presented persistent thirst. None presented elevation of liver enzymes.

Conclusions

Chronic tolvaptan therapy is safe and can maintain strict eunatremia in patients with chronic SIADH. Progressively lower doses are needed, thus contributing to economic sustainability of therapy. The minimum dose is usually attained after 6 months of therapy. Oncological patients require higher doses, and pharmacological patients lower ones.

DOI: 10.1530/endoabs.37.EP673

EP674

Results of molecular genetic studies for determination of latent mosaicism and parental origin of X chromosome in girls with Turner syndrome in Uzbek population

Ravshan Mukhamedov, Nilufar Ibragimova & Malika Mirkhaidarova
Laboratory of Genomics under the Institute of Bioorganic Chemistry, Republic of Uzbekistan Academy of Sciences, Tashkent, Uzbekistan.

Goal

Identification of latent mosaicism and determination of a parental origin of an X chromosome in TS patients in Uzbek population.

Methods

Molecular genetic studies are carried out in 35 patients with TS (26 with monosomy and nine with mosaicism) at the age of 7–16 and their parents with a set of DIATOMTMDNA prep 200 reagents. DNA amplification was performed in Applied Biosystems thermocyclers. PCR products were subjected to electrophoresis on 12% acrylamide *bis*-acrylamide gel (29:1) with subsequent DNA staining with ethidium bromide and visualization by a BioDocAnalyze (Biometra) system.

Results

Three X-linked markers (DMD 49, AR and DX1283E) were studied on the basis of their high level of heterozygosis (varying from 88.6 to 93.3%), a number of alleles (11–19) and localisation both on a short and long X chromosome arm. The results obtained confirm that the use of a set of these primers (DMD 49, AR and DX1283E) will allow enhancing a probability of obtaining an informative marker and detection of latent X-mosaicism. Monozygosity on all three markers indicates the presence of only one X chromosome that in female patients will correspond to true monosomy (X0). Heterozygosis of one marker suggests on the presence of an additional second X chromosome or a part of an X chromosome which is observed both in 46XX karyotype (healthy) and in mosaic variants of chromosomal anomalies (45X0–46XX and 45X0–46XY).

Conclusions

A comparative analysis of polymorphic markers in TS patients and their parents enable us to establish the origin of an X chromosome and determine in gametogenesis of which parents meiotic impairment occurred. Identification of mosaicism in Turner syndrome is very important from the viewpoint of setting correlations between a phenotype and karyotype.

DOI: 10.1530/endoabs.37.EP674

EP675

Inferior petrosal sinus sampling in ACTH-dependent Cushing's syndrome: experience of a Tertiary Portuguese Hospital

Ana Coelho Gomes[1], Lia Lucas Neto[2], Maria Raquel Carvalho[1], Eduardo Barreiros[1], José Maria Aragüés[1], Luís Barreiros[1], Jorge Campos[2] & Mário Rui Mascarenhas[1]
[1]Endocrinology, Diabetes and Metabolism Department, Santa Maria Hospital, Lisbon, Portugal; [2]Neuroradiology Department, Santa Maria Hospital, Lisbon, Portugal.

Introduction

Cushing's disease (CD) is responsible for 80% of endogenous Cushing's syndrome (CS). However, distinguishing the cause of ACTH-dependent CS – CD vs ectopic CS – can be extremely difficult. Bilateral inferior petrosal sinus sampling (IPSS) has the highest diagnostic accuracy in this evaluation.

Objectives

The aims of this study were to determine the accuracy of bilateral IPSS in the differential diagnosis of ACTH-dependent CS and in predicting adenoma lateralisation in CD.

Design

We retrospectively analysed the ACTH levels in inferior petrosal sinus and peripheral blood samples of eleven consecutive patients with ACTH-dependent CS that performed bilateral IPSS between 2005 and 2014 in Santa Maria Hospital in Lisbon. ACTH levels from both inferior petrosal sinus and peripheral blood were measured before and after corticotropin-releasing hormone (CRH) administration – $0'$, $5'$, $10'$, and $15'$. Ratios of central-to-peripheral and interpetrosal ACTH levels were calculated.

Results

IPSS was uneventfully performed in the eleven patients and it was suggestive of CD in nine patients, ectopic CS in one patient and inconclusive in another one. Concerning the nine patients with CD, the basal IPSS central-to-peripheral ACTH ratios were diagnostic for CD (>2) in eight patients (88.9%) and the post-CRH IPSS central-to-peripheral ACTH ratios were diagnostic for CD (>3) in nine patients (100%). ACTH lateralization was found (interpetrosal ratios ≥ 1.4) in eight patients (88.9%). In the patient with ectopic ACTH CS, the IPSS pre- and post-CRH ACTH ratios were negative, as expected. Transsphenoidal surgery was performed in seven of the nine patients with CD and the histologic examination confirmed the diagnosis of ACTH-secreting pituitary adenoma in all of them. Two patients are waiting for surgery.

Conclusion

IPSS was a safe and well-tolerated procedure in our study group. It was effective in the differential diagnosis of ACTH-dependent CS and useful in planning CD surgical therapy.

DOI: 10.1530/endoabs.37.EP675

EP676

Placental IGF1R–PI3K/Akt pathway and its relationship to idiopathic birth weight alterations

Maria-Luisa Lazo-de-la-Vega-Monroy[1], Martha I González-Domínguez[1], Leonel Daza-Benítez[2] & Gloria Barbosa-Sabanero[1]
[1]Health Sciences Division, Medical Sciences Department, University of Guanajuato, Leon Campus, León, Guanajuato, Mexico; [2]UMAE, No. 48 IMSS, León, Guanajuato, Mexico.

Introduction

Alterations in foetal growth lead to neonatal health risks and favour metabolic diseases during adult life. Therefore, the study of birth weight determination and its modifications is crucial for metabolic diseases prevention. Placental growth is a key factor in foetal growth. It has been suggested that insulin and the IGF system play an important role in foetal growth and placental development and function. Although, insulin and IGFs in the umbilical cord blood have been associated to birth weight, the roles of placental IGF1 and insulin receptors (IGF1R and IR), and the PI3K/Akt signalling pathway, shared by both receptors, are not fully elucidated. We aimed to analyse protein expression of insulin/IGF receptors and activation of the PI3K/Akt pathway in relation to placental weight and birth weight.

Methods

Transversal comparative study in placentas from healthy mothers of term newborns small gestational age (SGA), adequate gestational age (AGA), and large for gestational age (LGA) ($n=20$/group). Protein expression of IR, IGF1R, and phosphorylation of signalling molecules were analysed by western blot.

Results

IGF1R expression decreased 20% significantly in SGA compared to control AGA, and positively correlated with placental weight ($r=0.34$, $P=0.007$) and birth weight ($r=0.285$, $P=0.027$). IR protein expression was not modified between groups. Phosphorylation of PDK1, main kinase for Akt activation, decreased 40% in both SGA and LGA compared to control. In line with this, we observed a nearly 30% decrease in total Akt in SGA and LGA compared to AGA. PDK1-dependent phosphorylation pAkt–Thr308 showed a tendency, albeit not significant, to decrease in SGA and LGA, while pAkt–Ser273 did not differ between groups.

Conclusion

These results suggest PI3K/Akt pathway may be differentially regulated in SGA and LGA placentas, possibly related to decreased IGF1R expression in SGA, and

perhaps other signalling pathways in LGA, consequently leading to alterations in birth weight.

Disclosure
This work was supported by the University of Guanajuato (0095/13), and FOMIX CONACYT – Guanajuato State Government (GTO-2012-C03-195238). M-L Lazo-de-la-Vega-Monroy was recipient of a postdoctoral fellowship scholarship from CONACYT (CVU: 217876).

DOI: 10.1530/endoabs.37.EP676

EP677

The impact of correcting the serum sodium level for total proteins in patients receiving parenteral nutrition

Emilia Gomez Hoyos[3], Pilar Matia Martin[2], Martin Cuesta Hernandez[1], Teresa Ruiz Gracia[2], Natalia Perez Ferre[2], Lucio Cabrerizo Garcia[2], Miguel Angel Rubio Herrera[2], Daniel De Luis Roman[3], Alfonso Calle Pascual[2] & Isabelle Runkle de la Vega[2]
[1]Beaumont Hospital, Dublin, Ireland; [2]Clinico San Carlos Hospital, Madrid, Spain; [3]Clinico Universitario de Valladolid, Valladolid, Spain.

Introduction
In a majority of Spanish hospitals, serum sodium levels (SNa) are determined by indirect electrode methodology (sodium in the liquid fraction of serum) divided by the total serum volume (mmol/l). To avoid over/underestimating SNa, a formula can be applied: SNa corrected for total proteins (TP) = SNa × 93 divided by (99.1 − (0.7 × TP)). Hypoproteinaemia is frequent in patients receiving parenteral nutrition (PN), and is probably related to surgery, acute disease, and malnutrition. We have evaluated the impact of hypoproteinaemia on the frequency and degree of hyponatremia in PN patients.
Methods
A retrospective study of patients prescribed PN from 01/11/11 to 01/06/12. SNa was determined at baseline and during PN, and corrected for TP. All sodium levels were corrected for glycemia and presented in mmol/l. Patients with triglycerides >400 mg/dl were excluded. Indirect SNa (SNa) was compared to SNa as corrected for TP (TP-SNa). χ^2, Student's, and Mann–Whitney *U* test.
Results
222 patients were prescribed PN, 57.2% of whom were men. The median age was 75 (61–82). 47.3% were on the general surgery ward, 12% internal medicine, 12.1% oncology, and 8.6% hematology. 14.5% presented malnutrition (by BMI). Median duration of PN was 8 (5–14) days. Average baseline TP was 5.25 (S.D.: 0.76), with 93% presenting hypoproteinaemia (TP <6.5 g/dl). Baseline SNa: 138.1 (S.D.: 4.5) ($P<0.001$), TP-SNa: 134.6 (S.D.: 4.5) with a difference of 3.5 mmol/l (95% CI: 3.4–3.6) ($P<0.001$). 20% presented initial hyponatremia (SNa <135 mmol/) vs 52% (TP-SNa <135) ($P<0.001$). 28.7% developed SNa hyponatremia during PN, vs 64.2% with TP-SNa ($P<0.001$), within 4 (2–7) and 3 (1–14) days respectively ($P=0.05$).
Conclusions
Patients receiving parenteral nutrition often present hypoproteinaemia. Therefore, correction of indirect SNa for total proteins becomes essential, both to avoid underestimation of the number of patients with hyponatremia, as well as to correctly take into account its degree.

DOI: 10.1530/endoabs.37.EP677

EP678

Long-term safety, tolerability, and efficacy of extended release somatostatin analogues

Javier González, Rogelio García-Centeno, María Arnoriaga, María Picallo, María Laura Ramírez, Victor Manuel Andía, Yoko Lucía Olmedilla, Aurelio López & Susana Monereo
General University Hospital Gregorio Marañón, Madrid, Spain.

Introduction
The main indications for the somatostatin analogues (SST-A) are acromegalies and/or neuroendocrine tumors. They can increase fecal fats, which could lead to the loss of fat soluble vitamins. There are few published studies showing the effects of the long-term use.
Methods
Retrospective study of patients with SST-A indicated from our endocrinology department in the last 10 years. We analysed indications and different epidemiological, clinical, and laboratory data, at baseline and after treatment with SST-A. Results expressed as: percentages (qualitative variables), average and S.D. (quantitative variables), with a significance level of $P<0.05$.
Results
39 patients (66.6% women and 33.3% men) of 57.5 (13.68) years. Indications: acromegaly 71.8%, gastroenteropancreatic NETs 15.4% (four MEN1, one VHL, and one sporadic), gigantism 5.1%, advanced medullary thyroid cancer 2.6%, Graves' ophthalmopathy 2.5% and thoracic neurofibroma in NFI 2.6%. 69.2% was treated with octreotide LAR average dose of 44.73 (32.27) mg/28 days and 25.6%, with lanreotide Autogel 46.5 (35.88) mg/28 days or both 5.1%. Durability of 57.12 (13.68) months. 7.6% were cured, 79′58% controlled the disease, 12.82% had persistent disease (two acromegalies and three NETs progressed). Side effects: gastrointestinal 17.9%, biliary 20.5% (7.69% asymptomatic cholelithiasis, 2.6% symptomatic cholelithiasis, and 10.3% cholecystectomy), and 2.6% post-injection reactions. Analytical changes after treatment: HbA1c 6.3% (3.20) vs 6.5% (3.02), *P* 0.008; AST 18.02 (6.97) vs 24.87 (25.78), *P* 0.008; GGT 31.89 (44.09) vs 76.52 (160.75), *P* 0.075, and FA 98 (68.92) vs 149.34 (202.74), *P* 0.06. There were no significant differences in other analytical or vitamin parameters. 12.6% of patients discontinued treatment for: healing 7.6%, intolerance 2.5%, and ineffectiveness 2.5%.
Conclusions
SST-A are effective and well tolerated drugs. We found no evidence of malabsorption due to its use. Most frequent adverse effects were digestive, hepatobiliary and glycemic alterations, as described in the literature.

DOI: 10.1530/endoabs.37.EP678

EP679

Hyponatremia and mortality in patients hospitalised for heart failure (2005–2011)

Javier Marco[1], Irene Crespo[1], Ana Ortolá[1], Teresa Ruiz Gracia[1], Paz De Miguel[1], Manuel Mendez[1], Karla Nuñez[1], Judith Lopez[2] & Alejandra Duran[1]
[1]Hospital Clinico San Carlos, Madrid, Spain; [2]Hospital Universitario de Canarias, San Cristobal de la Laguna, Spain.

Introduction
Hyponatremia is the most frequent electrolyte disorder in hospitalised patients. Our aim was to determine the incidence, mean hospital stay, readmission rate and mortality rate among patients with acute heart failure (HF) and hyponatremia.
Methods
Retrospective analysis of data collected from the minimum data set (MDS) of Spanish National health System during 2005–2012 from discharged patients of Internal Medicine with HF and hyponatremia. A bivariate analysis was conducted in order to detect differences in the mortality rate, mean hospital stay and readmission. A logistic regression analysis was performed using as dependent variable in hospital mortality, adjusted for age and Charlson's index. χ^2 and Student's *t*-tests were performed.
Results
A total of 11 095 (2.2%) out of 504.860 cases with HF presented hyponatremia and 64.6% were women. Mean age was 81.9 (S.D.: 9.27) years in hyponatremia groups vs 79.7 (S.D.: 9.76) in normonatremic patients. In our study we found an increased prevalence of encoded hyponatremia as the mean diagnosis, from 7.7% in 2005 to 24.4% in 2011. The overall mortality in hyponatremic patients was 17.5% vs 10.9% ($P<0.001$) in non hyponatremic. Readmission rate was 22.2% vs 16.8% ($P<0.001$). Hyponatremia was associated with an increased risk of mortality, with an OR 1.58 (95% CI 1.50–1.66); $P<0.05$. The same results were found in the logistc regression analyses adjusted for age (OR 1.061 (95% CI 1.060–1.062); $P<0.05$) and for Charlson's index (OR 1.388 (95% CI 1.361–1.461); $P<0.05$).
Conclusions
Hyponatremia was associated with an increased mortality risk in hospitalised patients with HF, as described in previous studies. Thus, its accurate diagnosis and treatment is crucial. Nowadays, hyponatremia is considered to be a mayor diagnosis as reflected in the increased prevalence of its coding in discharged sheets. Nonetheless, further prospective studies regarding hyponatremia and mortality are needed.

DOI: 10.1530/endoabs.37.EP679

EP680

Giant prolactinoma: a current challenge

Ana Pires Gonçalves[1], Ana Rita Clara[2], Artur Lourenço[3], Miguel Cordeiro[4], Rui Almeida[2] & Mário Lazaro[2]
[1]Internal Medicine Service, Endocrinology's Division, CHAlgarve, Faro, Portugal; [2]Internal Medicine Service, CHAlgarve, Faro, Portugal; [3]Neurosurgery Service, CHAlgarve, Faro, Portugal; [4]Neuroradiology Service, CHAlgarve, Faro, Portugal.

Introduction
Giant prolactinomas are rare tumours, representing 2–3% of all prolactin (PRL)-secreting tumours. Their definition is restricted to pituitary adenomas with a diameter $\geq$4 or $\geq$2 cm of suprasellar extension, very high PRL concentrations ($\geq$1000 ng/ml) and no concomitant GH or ACTH secretion. They are more common in young to middle-aged men. Endocrine symptoms are often present for a long period of time, but most times the diagnosis is made when neurologic complications occur.
Purpose
We present a rare case of giant prolactinoma and review related literature.
Clinical case
The patient is a 40 years old male, with no personal or family history of endocrinopathy. On July 2014 he rushed to the Emergency Department at CHAlgarve due to a change in behaviour, confusion and loss of sphincter control occurring over the previous 2 days. The sellar-MR showed a mass with 68×46×50 mm, intense contrast enhancement, involving intra and left parasellar with hydrocephalus and erosion of bone pavement. The patient underwent ventriculoperitoneal drainage and was admitted in the neurosurgery department. The laboratory study showed PRL >2000 ng/ml (3.46–19.40 ng/ml) and free testosterone 3.1 pg/ml (7.20–23 pg/ml). He started cabergoline 0.5 mg/day, two pills per week. While recovering in the ward it was possible to establish a 2 years of progressive worsening headache, left lateralized, about 1-month, diplopia, right hemianopsia and symptoms of hypogonadism. One month after starting therapy he presented with rinorraquia, needing an endoscopic intervention to repair the sellar pavement. Patient re-evaluation after 6 weeks therapy revealed a 29.4% tumour diameter reduction and after 5 months a significant symptomatic improvement occurred, with normalisation of PRL and testosterone.
Conclusion
In patients with giant invasive pituitary adenoma it is important to evaluate pituitary function. Clinicians should be aware of hook effect. Although naïve or acquire resistance to dopaminergic agonists are most frequently in these tumours, medical therapy should be considered as first-line treatment in most patients.

DOI: 10.1530/endoabs.37.EP680

EP681

Clinical case of TSH-secreting pituitary adenoma

Anna Lipatenkova[1], Larisa Dzeranova[1], Ekaterina Pigarova[1] & Liudmila Astafieva[2]
[1]Endocrinology Research Centre, Moscow, Russia; [2]Burdenko Neurosurgery Institute, Moscow, Russia.

TSH-secreting pituitary adenoma (thyrotropinoma) is a rare (0.5% of all pituitary adenomas) and usually benign pituitary lesion, arising from the monoclonal expansion of neoplastic thyrotrophes. Thyrotropinoma usually presents with symptoms thyrotoxicosis (milder compared to those originating from the primary thyroid disorders) and mass effects of the pituitary tumour.
Aim
To describe the clinical course of thyrotropinoma presented with paroxysmal atrial fibrillation with high sensitivity to somatostatin analogues.
Case presentation
In a 53 years old man the disease manifested in 2001 at the age of 41 years with paroxysmal atrial fibrillation and hypertension effectively medically treated with β-blockers. The paroxysms were well controlled but became a lot frequent since December 2013. The hormonal profile showed elevated levels of TSH – 4.3 μU/ml (0.25–3.5), FT_4 – 23.56 pmol/l (9.0–20.0), FT_3 – 7.63 pg/ml (2.5–5.5), and normal levels of IGF1, ACTH, cortisol, LH, and FSH. Thyroid autoantibodies were negative. Ultrasound revealed diffuse changes without increasing the thyroid gland size, MRI demonstrated a pituitary macroadenoma 18×12×11 mm with para(D)-sellar extension. Test with short acting octreotide showed normalization of TSH, FT_4, and FT_3 levels during the first week of treatment. Subsequent therapy with octreotide LAR was started with dose 10 mg once in 28 days with further induction of euthyroidism, decrease of vertical size of pituitary adenoma on MRI at 5 months of medical treatment. Subjectively, the patient noted an improved health with disappearance of atrial fibrillation paroxysms. In 2014 the patient underwent a transnasal adenomectomy. The immunohistochemical analysis of the removed tumor showed positive staining for TSH, GH, SSTR2, and SSTR5. One week after surgery, TSH was suppressed. Postoperative laboratory tests 1 month after surgery confirmed euthyroidism: TSH – 2.21 μU/ml (0.4–4.0), FT_4 – 11.1 pmol/l (9.0–20.0), and FT_3 – 5.3 pg/ml (2.3–6.3).
Conclusion
The TSH-secreting adenoma is a rare cause of hyperthyroidism. Diagnosis is usually delayed due to milder and nonspecific clinical picture, because of that patients can be managed by cardiologists for long periods of time. Surgery is still the mainstay of treatment, although somatostatin analogues may be effectively used as medical therapy which is reflected by expression somatostatin receptors in the adenoma.

DOI: 10.1530/endoabs.37.EP681

EP682

Granins (chromogranin A, secretogranin II, and secretoneurin) as biochemical and immunohistochemical markers of non-functioning pituitary adenomas

Anna Lipatenkova[1], Larisa Dzeranova[1], Ekaterina Pigarova[1], Liudmila Astafieva[2], Liudmila Shishkina[2] & Anastasia Ektova[3]
[1]Endocrinology Research Centre, Moscow, Russia; [2]Burdenko Neurosurgery Institute, Moscow, Russia; [3]Russian Pediatric Clinical Hospital, Moscow, Russia.

Objective
To assess the sensitivity of granins – chromogranin A (CgA), secretogranin II (SgII), and secretoneurin (Sn) as biochemical and immunohistochemical markers of non-functioning pituitary adenomas (NFPAs):
Methods
50 patients with NFPAs were included in the study. Tissue samples were immunostained for pituitary hormones, Ki-67, αSU, CgA, SgII, and Sn. Furthermore, we have determined the levels of CgA, SgII in the serum and Sn in the plasma samples by ELISA method in patients before and after surgical treatment.
Results
Of the 50 NFPA 27 (54%) were gonadotropic tumours, 12 (24%) were null cell adenomas, immunopositivity for ACTH was determined in six cases (12%), for GH in four cases (8%), and for PRL in one case (2%). The median level of Ki-67 was 2.8% (min. 0.2% and max. 7%). We divided all patients in four groups by the degree of granin immunopositivity. High immunopositivity for CgA was found in ten cases (21%), for SgII in 17 (34%), for Sn in 24 (52%) compared to negative staining in 8 (17%), 10 (20%), and 2 (4%) respectively. High immunopositivity for all granin types was more frequent in gonadotropinomas, negative or slow staining for CgA and medium to high staining for SgII and Sn was more typical for ACTH and GH silent adenomas. The average serum CgA concentration before operation was 60.3 nmol/l (±5.2), after surgical treatment 67.84 (±9.8), SgII serum 24.9 (±8.9) and 27.6 (±8.9), plasma Sn 3.2 (±0.2) and 3.4 (±0.3) serum respectively. In healthy subjects the average levels of CgA and Sn were comparable with NFPAs patients 60.2 (±10.5) and 4.1 (±0.7), respectively, but healthy subjects had lower levels of SgII 14.8 (±7.30). We did not found any correlation between granin levels and their tissue expression.
Conclusions
Our work shows that a majority of NFPAs are truly secreting adenomas with significant numbers comprising potentially hazardous cortico- and somatotropinomas. CgA, SgII, and Sn have a high expression in most of the NFPAs, but their serum/plasma levels before and after surgical treatment were not much different from the controls and did not correlate with immunohistochemical results. So serum CgA and plasma SN measurement do not represent a helpful biochemical marker of NFPAs potential hypersecretion, except of SgII, but this requires further study on a large sample of patients.

DOI: 10.1530/endoabs.37.EP682

EP683

The role of tolvaptan in syndrome of inappropriate antidiuretic hormone secretion: clinical outcomes and effect on length of stay

Yolanda López Vázquez, María Barragans Pérez, Cristina Trigo Barros, Ángel Martínez González, Javier Lago Garma & Concepción Páramo Fernández
Complexo Hospitalario Universitario de Vigo (EOXI), Vigo (Pontevedra), Spain.

Introduction
Hyponatremia is the most common electrolyte imbalance among hospitalised patients. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is considered the most frequent etiology on patients with euvolemic hiponatremia. Conventional treatment includes water restriction and salt tablets with limited efficacy and very slow onset of action in certain patients.
Material and methods
Systematic sampling of all SIADH patients treated with tolvaptan (group A, $n=12$) in our service over the last 2 years was compared to 12 within the conservative treatment group (group B). The average age was similar in both groups (A: 71.8 years vs B: 71.6 years) with a clear male predominance in the whole sample. The average plasma sodium was also similar (A: 123.4 mmol/l vs B: 123.8 mmol/l). SIADH etiology was mainly neurosurgical (A: nine patients and B: seven patients).
The length of hospital stays was compared with the time span until natremia normalization in both groups. The variables are expressed as mean $\pm$ S.D. The statistical analysis used was Student's *t*-test. P value <0.05 was considered significant.
Results
The length of hospital stay from the beginning of the treatment was 11.1 ± 8.1 days in the tolvaptan-treated group and 16.7 ± 11.5 days in the conservative-treatment group ($P=0.18$). The mean hospital stay was higher for those treated with conservative therapy. Normalisation of natremia took 2.7 ± 2.7 days in the tolvaptan-treated group and 11.3 ± 9.4 days in the conservative-treatment group. The speed of correction of the hyponatremia was statistically significant for those in the tolvaptan-treated group ($P=0.04$).
Conclusion
Tolvaptan treatment in SIADH patients shows a rapid normalisation of natremia, effectively reducing inpatient length of stay.

DOI: 10.1530/endoabs.37.EP683

EP684

Opposite effects of dexamethasone and retinoic acid on neuronal actin cytoskeleton

Hélène Roumes[1], Julie Brossaud[1,2], Marie-Pierre Moisan[1], Véronique Pallet[1], Anabelle Redonnet[1] & Jean-Benoît Corcuff[1,2]
[1]UMR 1286 INRA Univ. Bordeaux, Bordeaux, France; [2]University Hospital, Bordeaux, France.

Brain ageing associates decreased neuronal plasticity, increased glucocorticoid and decreased retinoic acid (RA) signalling. We previously showed an interaction of these pathways on the regulation of a synaptic plasticity gene, BDNF. We thus investigated the effects of GC and RA on two BDNF-dependent genes: activity-regulated cytoskeleton protein (Arc) and Ca^{2+}/calmodulin-dependent protein kinase II (CaMK). Dexamethasone (Dex, 10^{-6} M) and/or RA (10^{-6} M) were applied on HT22 hippocampal cells during 4 days. Dex significantly decreased (55%) whereas RA increased cellular (145%) CaMKII mRNA compared to control. When combined RA reduced Dex effect. Dex alone did not affect (95%) whereas RA increased (195%) Arc mRNA levels. When combined to Dex RA had the same effect on Arc mRNA as when used alone. As plasticity is closely related to the formation of cell processes, we investigated cell morphology and F-actin cytoskeleton organisation. Dex affected cell morphology: Dex-treated cells areas were significantly larger and rounder than controls and these increases were suppressed when RA was added. Actin expression (mRNA) and abundance (protein) were unchanged by Dex or RA.
Conversely, phalloidin-stained polymerised actin was doubled by Dex. RA suppressed this effect. Both cortical actin and stress fibres were significantly increased by Dex (276% of control). RA suppressed this effect down to the level attained with RA alone: either moderately increased (190%) for cortical actin or decreased under control level for stress fibres (79%). Both glucocorticoids and RA target cell actin cytoskeleton and subsequently cell remodelling. The positive effects of RA on memory processes may then be due to counteracting some of the deleterious effects of glucocorticoids observed in brain ageing.
Disclosure
This study was supported by the Conseil Régional d'Aquitaine and the University of Bordeaux1.

DOI: 10.1530/endoabs.37.EP684

EP685

The relationship of genetic factors to the development of nephrolithiasis in primary hyperparathyroidism

Elena Peretokina[1], Natalia Mokrysheva[1], Lyudmila Rozhinskaya[1] & Ekaterina Zakharova[2]
[1]Endocrinology Research Center, Moscow, Russia; [2]Medical Genetics Research Center, Moscow, Russia.

Factors affecting the development of nephrolithiasis (NL) in primary hyperparathyroidism (PHPT) actively studied. CASR polymorphisms may be linked with the development of NL in PHPT. Supposed to the role of VDR in the development of nephrolithiasis in patients without PHPT.
Objective
To assess the relationship of polymorphisms CASR and VDR with the development of the NL at PGPT.
Methods
The study included 187 patients with PTPT (54 (49; 64) years), 110 with NL and 77 without NL. The study of polymorphisms CASR (R990G, A986S, and Q1011E). In 166 patients (110 with NL and 56 without NL) were analyzed polymorphisms VDR – ApaI, BsmI, FokI, Cdx2, and TaqI. The distribution of genotypes consistent with the condition of Hardy–Weinberg.
Results
The most common in both groups were polymorphisms R990G (23.6% vs 21.8%) and A986S (29.1% vs 37.9%), and Q1011E (16.4% vs 9.2%) met the most rare, the differences are not reliable ($P>0.05$). The genotype distribution was as follows CASR, with NL: AA-70.9%, AS-23.6%, SS-5.5%; RR-76.4%, RG-20.9%, GG-2.7%; QQ-83.6%, QE-14.5%, and GG-1.8%; without NL: AA-62.1%, AS-32.2%, SS-5.7%; QQ-90.8%, QE-8.0%, EE-1.1%, RR-78.2%, RG-19.5%, and GG-2.3%; not obtained differences in the frequency of genotypes and alleles CASR between the groups ($P>0.05$). VDR polymorphisms frequency did not differ between the groups ($P>0.05$). with NL: allele A-54.9%, a-45.1%; allele B-65.5%, b-34.5%; allele F-61.2%, f-38.8%; allele G 84.5%, A-15.5%; allele T-61.2%, and allele t-38.8%. In the group without NL: allele A-55.4%, a-45.5%; allele B-65.5%, b-59.6%; allele F-55.7%, f-44.3%; allele G-86.6%, A-13.4%; allele T-55.7%, and t-44.3%. The distribution of genotypes and alleles of VDR polymorphisms in the presence and absence of NL was not significantly different ($P>0.05$).
Conclusion
According to the results revealed a high prevalence of polymorphisms of VDR and CASR patients with PHPT. Development of NL is not associated with the presence of VDR polymorphisms and CASR.
Disclosure
The work was supported by grant of President of Russian Federation Н Ш -4527.2014.7.

DOI: 10.1530/endoabs.37.EP685

EP686

Pineal gland and thymus: structural and functional unity

Michael Paltsev[1], Igor Kvetnoy[2], Victoria Polyakova[2], Natalia Linkova[2] & Tatiana Zubareva[2]
[1]Russian Academy of Science, Moscow, Russia; [2]Ott Institute of Obstetrics and Gynecology, Saint-Petersburg, Russia.

Neuroimmunoendocrine changes of the pineal and thymic function, are now believed to pay an important role in the mechanisms of age-associated diseases development. Here we studied the morphofunctional and signal molecules unity of pineal gland and thymus during ageing. Autopsic pineal gland and thymus

material sampled from people was divided into groups 1 – middle-aged people (60–74 years) and 2 – old people (75–89 years). Ultra-thin slices were used for electron microscopy. The study was carried out on the electron microscope JEM-100S. The identification of markers of signal molecules serotonin, melatonin, CD8, CD20 was carried out with immunohistochemical method using primary mouse MABs, and secondary antibodies, biotinylated anti-mouse immunoglobulins. The data of electronic microscopy had shown the ultrastructure similarity of pinealocytes and thymic epithelial cells (TEC) in autopsy samples of pineal gland and thymus. Pinealocytes and TEC have the high number of round vesicules with, as we suppose, can consist biological activity signal molecules, in pinealocytes and TEC cytoplasm. These data can show that the both types of cells can belong to neuroimmunoendocrine system. By immunohistochemical method it was verified the expression of common signal molecules – endocrine cells markers (melatonin, serotonin) and lymphocytes (CD8, CD20) in the human pineal gland and thymus. The expression of melatonin, serotonin, CD8, CD20 in the pineal gland and thymus decreased during aging.
Thus, the melatonin, serotonin CD8, CD20 expression in the pinealocytes and thymic cells confirms the unity of pineal gland and thymus as an neuroimmunoendocrine organs.

DOI: 10.1530/endoabs.37.EP686

EP687

Serum melatonin levels in pharyngo-laryngeal carcinomas

Adina Zamfir Chiru Anton[1], Dana Manda[2], Radu Cristian Popescu[3] & Dan Cristian Gheorghe[4]
[1]Childrens' Hospital Grigore Alexandrescu, Bucharest, Romania; [2]C.I.Parhon National Institute of Endocrinology, Bucharest, Romania; [3]Coltea Clinical Hospital, Bucharest, Romania; [4]Childrens' Hospital M.S. Curie, Bucharest, Romania.

Background
Melatonin is mostly known as a circadian hormone, but it also has effects in a large number of cellular processes (cell differentiation, proliferation, apoptosis, redox balance). Although it was studied in many tumours, very little is known about his role in pharyngo-laryngeal carcinomas.
Aim
To evaluate serum melatonin levels in patients with pharyngo-laryngeal malignant tumours preoperatively and after surgical excision of the malignancy.
Materials and methods
45 patients (41 men and four women, 59 ± 7.42 years) and 35 age-matched healthy subjects have been tested for melatonin levels using ELISA method after serum extraction by reverse phase chromatography. Each patient had two blood samples, one in the morning and one at midnight in order to record the day and night melatonin levels. 19 patients (42.2%) presented a laryngeal squamous cell carcinoma, 22 patients (48.8%) pharyngeal, base of tongue or tonsil squamous cell carcinoma, and four patients (9%) had other malignant tumours in the head and neck region. Patients with β-adrenergic blockers medication have been excluded.
Results
43.7% of the patients had a T1 stage tumour, while T2, T3 and T4 stages were recorded in 18.75, 25.05 and 12.5% respectively. Biopsy revealed a squamous cell carcinoma in 82.9% of the patients. Tumour patients have been monitored postoperatively and their melatonin secretion tested after surgery as well (2 days after the surgery). Before surgery, cancer patients had significant lower levels of melatonin compared to healthy subjects. There were no significant changes immediately after surgical removal of the tumours.
Conclusion
Serum melatonin levels are lower in patients harbouring a pharyngeal or laryngeal tumour compared to healthy subjects. The idea of long-term recording of melatonin levels in head and neck cancer patients treated by different therapeutical approaches and future possibilities of using melatonin substitution in therapy is discussed.
Disclosure
This work received financial support through the project entitled 'CERO – Career profile: Romanian Researcher', grant number POSDRU/159/1.5/S/135760, co-financed by the European Social Fund for Sectorial Operational Programme Human R.

DOI: 10.1530/endoabs.37.EP687

EP688

Plasma β-endorphins level is higher in lean patients with polycystic ovary syndrome than in lean women without this disorder

Marta Kialka[1], Magdalena Spalkowska[2], Tomasz Milewicz[1], Anna Pelka[3], Barbara Wasyl[4], Iwona Rogatko[5] & Rita Tomczyk[1]
[1]Department of Gynecological Endocrinology, Collegium Medicum, Jagiellonian University, Cracow, Poland, [2]Department of Dermatology, Collegium Medicum, Jagielonian University, Cracow, Poland, [3]Internal Disease Department, Dietl Specialist Hospital, Cracow, Poland, [4]Department of Pediatrics, L. Rydygiera Hospital, Cracow, Poland, [5]Department of Clinical Biochemistry, Polish-American Institute of Pediatrics, Cracow, Poland.

Introduction
Polycystic ovary syndrome (PCOS) is one of the most common causes of anovulatory and infertility. According to the widespread data it affects 3–10% of women in the procreative age. Although many research have been done, it is still unclear which of mechanisms are responsible for the development of PCOS. The most up-to-date scientific trial indicates that the evolution of PCOS is related to the activity of the endogenous opioid system but precise mechanism is not completely understood.
Description of methods/design
26 lean women (BMI $= 21.34 \pm 1.83$) were enrolled to the study and divided into two groups: group A consisted of 12 PCOS patients with FAI > 5 and group B consisted of 14 women without features of PCOS and with FAI < 5. Standard diagnostic hormone profile was made in all the patients and the level of β-endorphins was measured. The following hormones were measured: FT_3, TSH, FT_4, aTPO, aTG, LH, estradiol, testosterone, cortisol, DHEAS, prolactin in metoclopramide test, insulin in OGGT test, vitamin D3, C-peptide, CA125. BMI was assessed.
Results
Mean β-endorphin levels was significantly higher in group with FAI > 5 (14.73 pg/ml ± 4.97 vs 7.26 pg/ml ± 2.62; Mann–Whitney test; $P = 0.000018$). Spearman test indicated also a positive correlation between β-endorphin level and weight ($r = 0.682$; $P < 0.05$) and β-endorphin level and C-peptide level ($r = 0.778$; $P = 0.05$) in FAI < 5 group. Absence of the significant correlation was observed in FAI > 5 group. It might be a consequence of limited number of this group.
Conclusion
Our study showed that the level of β-endorphins was statistically significant higher in patients with PCOS. Further experimental research is required to evaluate the correlation between β-endorphins and PCOS evolution.

DOI: 10.1530/endoabs.37.EP688

EP689

Gene panel study for familial pituitary adenoma

Tatiana Borodich, Ekaterina Pigarova, Elena Przhiyalkovskaya, Larisa Dzeranova, Liudmila Rozhinskaya, Evgeny Vasilyev, Anatoly Tiulpakov & Ivan Dedov
Endocrinology Research Centre, Moscow, Russia.

Introduction
Several genetic syndromes are associated with familial pituitary adenomas. The penetrance of clinical manifestations of these syndromes is not ubiquitous and this might be the reason for the lack of detection of genetic mutations when only one or few genes are studied.
Aim
Clinical characterisation and molecular genetic study of a panel with ten genes involved in formation of pituitary adenomas in familial setting.
Materials and methods
Study included six families (13 patients) with familial pituitary adenomas with no other features of known genetic syndromes. Three families were with the homogeneous type of secretion (acromegaly) and three families with the heterogeneous type (acromegaly/nonactive pituitary adenoma). The study involved five men (38%) and eightt women (62%).
Results
Median age was 55.6 years (40–69 years), the average height for females was 160 cm, for males 170 cm. Most adenomas were GH-producing and non-secreting. The diagnosis of acromegaly was confirmed by hormone testing (GH $>$ 2.5 ng/ml $<$ no suppression on OGTT and high IGF1). Maximum GH was 23.9 ng/ml, medium -13.9 (0.42–23.9), IGF1: maximum – 1817, medium – 1517 (439–1817). Minimum size of adenomas was 7 mm, maximum – 17 mm.

Tumour extensions were: supra – (three cases, 23%), latero – (two cases, 15%). In most patients, adenomas were extended in more than 2 directions. Genomic DNA from a blood samples of patients (probands) underwent high-throughput sequencing on the Ion Torrent Personal Genome Machine (Life Technologies) using a custom-designed AmpliSeq panel for the sequencing of a panel of genes (MEN1, CDKN1B, PRKAR1A, GNAS, AIP, SDHA, SDHB, SDHC, SDHD, PRKCA, CDKN2C, CDKN2A, POU1F1, PTTG2) but no pathological mutations were detected.
Conclusions
Families with hereditary pituitary adenomas can have tumours with homogenous and heterogeneous types of secretion. We were not able to show any genetic alteration in the group of patients studied.
Disclosure
This work was supported by grant of the President of the Russian Federation MK-5411-2014.7.

DOI: 10.1530/endoabs.37.EP689

EP690

Quality of life in patients with acromegaly vs non-functioning pituitary adenomas and healthy control group

Aleksandra Jawiarczyk-Przybylowska[1], Dorota Szczesniak[2], Joanna Rymaszewska[2] & Marek Bolanowski[1]
[1]Department of Endocrinology, Diabetes and Isotope Therapy, Medical University, Wroclaw, Poland; [2]Department of Psychiatry, Division of Consulting Psychiatry and Neurobiological Research, Medical University, Wroclaw, Poland.

Objective
Acromegaly has an important impact on health-related quality of life. The aim of study was to ascertain the quality of life of patients with uncontrolled vs controlled acromegaly and compared to those with non-functioning adenomas and healthy control group.
Methods
124 participants underwent a cross-sectional assessment including the quality of life (AcroQoL, WHOQoL BREF), psychiatric morbidity (GHQ-28) and acceptance of illness (AIS). The sample consists of patients with acromegaly divided into two subgroups accordingly to minimal GH concentration during the OGTT or profile of GH and level of IGF1: controlled and cured acromegaly group (CAG $n=19$) and active acromegaly group (AAG $n=31$); patients with non-functioning adenomas group (NAG $n=37$) and healthy control group (CG $n=37$) matched according to age.
Results
No significant differences were identified between CAG, AAG and NAG groups referring to quality of life, psychiatric morbidity and acceptance of illness. Compared with healthy controls, AAG group suffered more from anxiety and insomnia ($P=0.031$) and had significantly poorer quality of life in psychological domain measured with WHOQoL BREF ($P=0.004$). In acromegaly group we observed statistically significant positive correlation between the level of IGF1 and prevalence of psychopathological symptoms measured by the GHO-28. We also observed negative correlation with the level of GH and AcroQoL in total score as well as in psychological dimension, including subscale '*appearance*'. The illness duration since diagnosis was identified as a negative predictor of physical dimension of AcroQoL ($r=-0.35$, $P=0.035$), social domain of WHOQoL ($r=-0.43$, $P=0.009$) and acceptance of the illness ($r=-0.42$, $P=0.011$).
Conclusion
Concerning the diagnosis, not only biochemical and radiological parameters, but also psychological aspect should be evaluated in acromegaly. IGF1 and GH could be an independent negative predictors of quality of life among those patients.
Disclosure:
Pbmn 118.

DOI: 10.1530/endoabs.37.EP690

EP691

Acute octreotide suppression test in acromegaly: predictive value in long-term response to long-acting somatostatin analogues

Ana Palha, Luisa Cortez, António Afonso, Fernando Fonseca & Ana Agapito
Centro Hospitalar Lisboa Central – Hospital Curry Cabral, Lisbon, Portugal.

Introduction
The usefulness of acute octreotide suppression test (OST) in the selection of patients with acromegaly for chronic somatostatin analogues (SA) treatment is still controversial.
Aim
To investigate the predictive value of OST for long-term responsiveness to long-acting SA.
Materials and methods
Retrospective study of 25 drug-naive patients (13 males) with active acromegaly, subjected to an OST (hourly serum GH concentrations for 8 h were measured before and after last administration of s.c. octreotide 100 μg q8 h for 48 h). The mean achieved GH was used for analysis. GH nadir response during OST was also evaluated. GH < 1 ng/ml and normal IGF1 (both evaluated as mean of three values) were used as parameters for biochemical control during SA therapy.
Results
On average, during OST a GH decline of $70.15 \pm 23.4\%$ was observed in this cohort. Most patients (72%; $n=18$) showed a decrease > 50% of GH during OST (group A), while 28% had ≤50% GH reduction (group B). During SA treatment, 61.1% of group A achieved IFG1 and/or GH normalization, with a mean reduction of 54.6 and 68.2% respectively. In Group B, 28.5% reached IFG1 and/or GH normalization, with a mean reduction of 42 and 52.7%, respectively. Biochemical control was observed in 11.1% of patients on group A and 14.3% on group B. In total, 36% of patients achieved a GH value < 1 ng/ml during the OST. In this group 77.8% ($n=7$) had mean reduction >50% during OST. This test showed positive (PPV) and negative predictive (PNV) values of 64.71 and 71.43% for 50% GH reduction and PPV (66.67%) and PNV (56.25%) for minimal GH level < 1 ng/ml during OST. A 50% reduction and a nadir GH < 1 ng/ml during OST didn't show correlation with the long-term normalisation of serum IGF1 and/or GH ($P=0.106$ and $P=0.271$ respectively).
Conclusion
In this cohort, a reduction of 50% and nadir GH < 1 ng/ml following an OST weren't predictive of remission on long-term SA as defined by updated criteria.

DOI: 10.1530/endoabs.37.EP691

EP692

Clinical experience in the treatment of acromegaly: 5 years follow-up results

Zelija Velija-Asimi[1] & Snjezana Pejicic[2]
[1]University Clinical Centre of Sarajevo, Sarajevo, Bosnia and Herzegovina; [2]Clinical Centre of Banja Luka, Banja Luka, Bosnia and Herzegovina.

The aim of this study was to evaluate our clinical experience in the treatment of acromegaly during 5-year follow-up period.
Methods
Seventeen acromegaly patients (11 women and six men) monitored during 5-year follow-up period. A level of GH of <2.5 ng/ml and the normal IGF range were considered as the criterion for remission. The GH level and IGF1 level were evaluated every 6 months, while magnetic resonance imaging was taken every year during follow-up period.
Results
All patients had growth in hands and feet and typical facial asymmetry in the beginning of the study. Six patients had diabetes mellitus (35%), four patients had hyperprolactinaemia (24%), two patients had hypothyroidism (12%) and five of patients had hypertension (29%). Visual field defect was in five patients (29%). Microadenomas founded in six patients and macroadenomas in 11 patients. Nine patients were treated by trans-sphenoidal surgery. One of them was cured, three patients developed postoperative pituitary deficiency. Two patients were treated by transcranial surgery, but not cured. One of them was treated by Gamma Knife radiosurgery and after that developed pituitary deficiency. Sixteen out of 17 acromegaly patients were treated by octreotide (six of patients as primary therapy and ten patients as secondary therapy after surgery). Biochemical remission was achieved in 12 of 16 patients (75%) who received octreotide treatment. Tumour size decrease was achieved in 54% of patients. The treatment was successful withdrawn at five patient (29%) without recurrence for 2–3 years follow-up. One patient passed away due to co-morbidities and at one patient treatment was cancelled due to kidney cancer. Only one patient (6.25%) who regularly used high dosage of octreotide has uncontrolled acromegaly.
Conclusion
Our findings demonstrated that octreotide LAR treatment successfully controlls clinical, biochemical and neuroradiological parameters.

DOI: 10.1530/endoabs.37.EP692

EP693

Fenofibrate has differential effects on cell proliferation and GH secretion in GH_3 cells

Sandra Rotondi[1], Alessio Modarelli[1], Patrizia Sanità[1], Adriano Angelucci[1] & Marie-Lise Jaffrain-Rea[1,2]
[1]Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy; [2]Neuroendocrinology, Neuromed, IRCCS, Pozzilli, Italy.

We have recently observed that the peroxisome proliferator receptor α was expressed by normal and tumoural pituitary tissues, in particular by somatotrophs. To elucidate its function, we have studied the effects of fenofibrate on cell proliferation and GH secretion in GH_3 cells.
Material and methods
GH_3 cells were grown in Ham's F10 and treated for 24, 48 and 72 h by different concentrations of fenofibrate (12.5–50 μM). Cells were counted and GH concentration was measured in the medium by ELISA. GH concentration was then corrected by cell number. Real time RT-PCR and western blotting were performed on RNA and protein extracts to further analyse GH transcription and intracellular content. Cyclophilin B, which expression was not influenced by fenofibrate, was used as a housekeeping gene and a protein load control. Data were analysed by ANOVA with *post-hoc* Tukey analysis. $P<0.05$ was considered significant.
Results
A significant time- and dose-dependent decrease in cell proliferation was observed in treated cells, with a simultaneous increase in GH concentration. GH increase was maximal at 48 h and reached about three-folds at 25 μM and four-folds at 50 μM ($P=0.004$ and $P=0.0004$ vs controls, respectively). Analysis of *GH* mRNA at 48 h showed a bimodal response, with a significant increase in gene transcription at 25 μM ($P=0.0094$) and levels similar to control cells at 50 μM ($P=0.002$ vs 25 μM). Compared to control cells, a modest increase in intracellular GH content was also observed at 25 μM, with a modest decrease at 50 μM, respectively.
Conclusion
Fenofibrate in its therapeutic concentration range is able to reduce cell proliferation in GH_3 cells, with a dose-dependent increase in GH secretion which may reflect either an increased in GH synthesis (at low dose) or an increase in GH release (especially at high dose). It may be of interest to evaluate the clinical implications of these findings, especially in acromegalics.
Disclosure
This work was supported by The Italian Ministry for University and Research (MIUR) Grant 2009YJTBAZ_002.
DOI: 10.1530/endoabs.37.EP693

EP694

Single dose irradiation of GH3 cells increase GH and PRL secretion in vitro

Amato Fratticci[1,2], Sandra Rotondi[1], Alessio Modarelli[1], Pierluigi Bonfili[2], Ernesto Di Cesare[1,2], Edoardo Alesse[1] & Marie-Lise Jaffrain-Rea[1,3]
[1]Department of Biotechnological and Applied Clinical Sciences; University of L'Aquila, L'Aquila, Italy; [2]Radiotherapy, S.Salvatore Hospital, L'Aquila, Italy; [3]Neuroendocrinology, Neuromed, IRCCS, Pozzilli, Italy.

Radiotherapy (RT) may represent a useful tool in the treatment of GH-secreting tumours in the presence of a post-operative active disease and single dose stereotactic RT/gamma knife is the preferred option in most cases. The effects of RT on the control of hormone secretion are very slow and pharmacological treatment remains necessary for years. Some authors advocate withdrawal of somatostatin analogues (SSA) during RT, although the short-term effects of RT on hormone secretion have been poorly studied. To address this issue, we used GH_3 cells as a model of GH-secreting tumours to evaluate the acute endocrine effects of a single irradiation dose.
Methods
GH_3 cells were treated with a LINAC and single 5 and 10 Gy irradiation were evaluated after 6, 24, 72 and 144 h in terms of cell proliferation and GH/PRL secretion/gene transcription by ELISA/Real Time RT-PCR assays.
Results
A significant time- and dose- dependent reduction of cell proliferation was observed in irradiated cells vs controls. In contrast, a significant time- and dose-dependent increase of GH and PRL release (ng/10^6 cells) was observed after 72 and 144 h in irradiated cells (up to five- and 11-fold at 10 Gy, respectively, $P<0.0001$ vs controls). A progressive time-dependent increase in PRL gene transcripts was observed in both irradiated and control cells, with a modest increase in irradiated vs control cells at 6 and 24 h. GH transcription also tended to increase immediately after irradiation, but was markedly reduced in irradiated cells at 72 and 144 h ($P<0.0001$ vs controls), suggesting a predominant effect of RT on GH release.
Conclusion
Transient increases in hormone secretion may occur after irradiation of GH/PRL-secreting cells, with potential differential effects in hormone synthesis and release. Such data should be evaluated in clinical practice in order to reconsider the indications for SSA withdrawal before irradiation in acromegalic patients.
DOI: 10.1530/endoabs.37.EP694

EP695

Associations between radiological parameters and molecular phenotype in human GH-secreting pituitary tumours: could they help in predicting the appropriate medical therapy?

Maria Rosa Alhambra-Expósito[1], María Sagrario Lombardo-Galera[3], Alejandro Ibañez-Costa[2], Esther Rivero-Cortés[2], Manuel Gahete[2], Raúl Luque-Huertas[2], María Ángeles Galvez-Moreno[1] & Justo Castaño-Pastor[2]
[1]Endocrinology and Nutrition Unit, Reina Sofia University Hospital, Córdoba, Andalucía, Spain; [2]Department of Cell Biology, Physiology and Immunology University of Córdoba, Córdoba, Andalucía, Spain; [3]Radiology Unit, Reina Sofia University Hospital, Córdoba, Andalucía, Spain.

Acromegaly is caused by excessive GH secretion from pituitary adenomas. Transphenoidal surgery is the first-choice treatment, but new drug therapies (e.g. somatostatin analogues, SSA) offer promising avenues for medical treatment. Complementary diagnostic tools may assist this strategy, helping to refine drug choice. Here, we investigate the associations between radiological features and molecular phenotype of pituitary tumours from acromegalic patients. This observational study included 17 acromegaly patients (38.4 ± 15.6 years; 64.7% women), diagnosed from 2007 to 2012 at the Endocrinology and Nutrition Unit of the Reina Sofia Hospital, in whom surgery, radiology and molecular phenotyping of the adenoma was carried out. Magnetic resonance was performed to localise the tumours, which were all macroadenomas (94.6%) at diagnosis except for one microadenoma. Anterior–posterior mean diameter (APD) was 18.3 ± 6.6 mm, inferior–posterior diameter (IPD) 18.8 ± 6.7, and left-right diameter (LRD) 17.9 ± 6.4 mm. Average volume was 33.36 mm^3. Extrasellar growth was observed in 73.3%, suprasellar growth in 60%, right sphenoid sinus invasion in 26.7%, left sinus invasion in 20%, and 20% in both sinus. Compared to isointense adenomas, T2 hyperintense tumours showed greater IPD (23.4 ± 5.3 vs 14.3 ± 5.4 $P=0.009$), LRD (21.2 ± 4.5 vs 14.6 ± 7.2 $P=0.035$), total volume (4.5 ± 2.6 vs 2.2 ± 3.1 $P=0.025$), and Knosp index (2.9 ± 1.2 vs 1.1 ± 1.5 $P=0.036$). T2 hyperintense adenomas had higher dopamine receptor subtype-5 (DR5) expression ($P=0.038$)) and Ki67 ($P=0.044$). Adenoma IPD directly correlated with expression of DR5 (Rho+0.770 ($P=0.006$)) and somatostatin receptor subtype-3 (sst3) (Rho+0.549 ($P=0.034$)); and DR5 expression correlated with APD (Rho+0.735 ($P=0.010$)). Adenoma volume was directly associated with sst3 (Rho+0.535 ($P=0.038$)) and DR5 (Rho+0.736 ($P=0.010$)) expression. Knosp index directly correlated with all diameters: APD ($P<0.001$), IPD ($P<0.001$), LRD ($P=0.002$); tumour volume ($P<0.001$); sst3 ($P=0.015$); and Ki67 ($P=0.044$). Our results reveal significant correlations among key pre-surgical radiological parameters and specific molecular phenotypic features of pharmacological relevance in GH-producing adenomas. Future studies should explore the molecular basis of these findings and their potential value in helping to select the appropriate medical therapy for these patients.
DOI: 10.1530/endoabs.37.EP695

EP696

Unravelling the role of stress regulators on GnRH release in Letrozole induced PCOS rat model

Nirja Chaudhari & Laxmipriya Nampoothiri
Department of Biochemistry, The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, India

Background and aim
polycystic ovarian syndrome is a multi aetiological female endocrinopathy wherein one of the major target organs affected is adrenal. It is important to note that adrenal plays key role in evoking stress mediated responses in brain; which can in turn affect GnRH, the main regulator of HPG axis. Along with corticotrophin releasing factor (CRF), newly discovered neuropeptides-urocortin2 and RF-amide related peptide-3 (RFRP-3) (mammalian GnIH analogue) are also known to modulate stress. However, complex regulation of GnRH axis via stress regulatory molecules and gonadal function adaptations is not clear. Thereby, current study was undertaken to elucidate the interaction of stress regulators with GnRH in PCOS pathology.
Material and methods
PCOS was induced in rat using letrozole-an aromatase inhibitor and confirmed for pathology. Hormones-gonadotropins, androgen, oestradiol, progesterone levels were measured by ELISA. Regulatory neurotransmitter-GABA was estimated by HPLC. Expression studies of GnRH regulatory neuropetides and their receptors-CRF1, CRFR1, Ucn2, CRFR2, GnRH, GnRHR, RFRP-3, GPR-147 were carried out using real-time PCR.
Results
Hypothalamus and pituitary of PCOS rats demonstrated an increase in corticosterone ($P<0.01$) and androgen levels ($P<0.01$) whereas progesterone ($P<0.05$) and estradiol ($P<0.01$) levels were decreased. These altered levels of steroids were parallel to changes obtained in their receptors (GR, AR, ER-α, ER-β, PR). GABA levels were significantly decreased in hypothalamus ($P<0.01$) and pituitary ($P<0.05$) with reduced GABAB1 receptor expression in PCOS rats. PCOS rats also showed significant alterations in mRNA expressions of Ucn2, RFRP-3 and GnRH1 with their receptors CRF2, GPR-147 and GnRHR, respectively.
Conclusion
This study elucidates the complex regulation of GnRH in the hypothalamus and pituitary by stress elements- Ucn2, RFRP-3 and their involvement in altered GnRH release in PCOS pathology.

DOI: 10.1530/endoabs.37.EP696

EP697

Patients with neuroendocrine neoplasms: the experience of a referral centre in Greece

Krystallenia Alexandraki, Georgios Boutzios, Eleftherios Chatzellis, Dimitrios Thomas, Maria Chrysochoou, Marina Tsoli, Maria Kaltsatou, Georgios Nikolopoulos, Panagiotis Moschouris & Gregory Kaltsas
Endocrine Unit, Department of Pathophysiology, Medical School, Laiko Hospital, University of Athens, Athens, Greece.

Introduction
Neuroendocrine neoplasms (NENs) are rare and heterogeneous neoplasms with variable biological behaviour but generally slow progression.
Methods/design
355 patients with NENs registered in our data-base have been studied (166 females, mean age: 52 years; range: 11–88), during the period 2004–2014. TNM system has been used for staging and proliferation index Ki-67 for grading.
Results
Out of 355 patients, 35 (10%) had neoplasms in the context of familiar disorders: MEN-1($n=32$) and Von Hippel Lindau ($n=2$). The following primary sites were registered: stomach: 56 (15.8%); duodenum: 13 (3.7%); pancreas: 131 (36.9%); small intestine: 40 (11.3%); appendix: 31(8.8%); colon: 14 (4%); lung: 27 (7.6%); thymus: 1 (0.3%), other sites: 22 (6.2%), unknown origin: 15 (4.2%); 4 (1.2%) had two concomitant neoplasms. 54 (15.3%) had functional syndrome. Metastatic deposits were found in 103 (29%) patients: bones: 16 (4.5%), lung: 5 (1.4%), liver: 94 (22.5%), peritoneum: 7 (2%), pancreatic: 2 (0.6%), brain: 2 (0.6%), omentum: 2 (0.6%), ovaries/kidneys/spleen: 1 (0.28%). 139 (47.8%) patients had Ki-67 $\leq$2% (grade 1), 111 (31.3%) 3–20% (grade 2), 24 (8.2%) $>$20% (grade 3) for gastro-intestinal NENs and for lung 4 (1.4%) atypical, 10 (3.4%) atypical, 1 (0.3%) large and 1 (0.3%) small cell lung carcinomas and 1 (0.3%) atypical thymic NEN. Stage1 were found in 135 (38.8%), stage2: 63 (18.1%), stage3: 48 (13.8%), stage4: 102 (29.3%). 197 patients had surgical removal of the neoplasms, 46 had an endoscopic resection. The other systemic or local therapies that the patients received as monotherapy or in combination as first line treatment are as following: somatostatin analogs ($n=100$), chemotherapy ($n=45$), neoplasm-targeted molecular therapy ($n=22$), radionucleotides ($n=9$), conventional radiotherapy ($n=6$), cauterisation with radiofrequencies/RFA ($n=8$), chemoembolisation ($n=6$), interferon ($n=2$). 99 patients received second, 44 third, 23 forth, 12 fifth, 5 sixth line treatment. In the last follow-up of the present analysis 21 patients died from their disease: five had grade1 neoplasm, ten grade 2, two grade 3, one atypical thymic and another atypical lung NEN but two patients did not have an available Ki-67.
Conclusion
The present registry imply that the majority of the patients with NENs have slow progression and long survival despite the presence of disseminated disease, confirming the necessity of the recent introduced therapeutic and diagnostic options following the guidelines as well as their management from referral centres under multidisciplinary teams.

DOI: 10.1530/endoabs.37.EP697

EP698

Review of assessment (diagnosis) of hyponatraemia

Penny Dhanjal[1] & Jayadave Shakher[2]
[1]Birmingham Heartlands Hospitals, Birmingham, UK; [2]Otsuka Pharmaceuticals UK Ltd., Wexham, UK.

Introduction
Hyponatraemia is the commonest electrolyte disorders encountered in hospitals. The aetiology of hyponatraemia is based on clinic assessment and biochemical investigations. However, studies have shown that recommended guidelines are usually not implemented.
Aim
Review of assessment (diagnosis) of Hyponatraemia and outcome based on length of stay (LOS) in hospitals.
Methods
A systematic search using PUB Med and Med Line, including an Internet search of published abstracts from British Endocrine Society, European Endocrine Society and Lung Oncology was conducted between 2002 and 2014 in UK hospital settings.
Results
18 publications were identified using search criteria using key word hyponatraemia combined with investigations, management and outcomes. Two were journal publications and the rest were abstract submissions which were of retrospective audit analysis of patients admitted with hyponatraemia in hospitals. Total of 2052 patients and the duration of the studies vary from 2 weeks to 52 weeks. There was wide variability with definition of hyponatraemia and S Na <130 and <125 mmol/l were commonly used. The aetiology diagnosis of SIADH was mentioned in all studies but only average score of 25% was recorded in all domains with regards to serum and urine osmolality and urine sodium. The average score improved to over 50% when cut off S Na was $<$ 125 mmol/l. The LOS was reported in nine studies and overall mean was 16 days.
Conclusion
Though the definition of hyponatraemia is <135 mmol/l, the audit findings seem to indicate there is higher threshold for detailed biochemical investigations when S Na is <125 mmol/l and to some extent when S Na falls to $<$ 130 mmol/l. This probably reflects under investigations with accurate diagnosis of hyponatraemia which would have an impact on management as shown in recent published study (Tzoulis *et al.*, *PGMJ* 2014;0:1–5).

DOI: 10.1530/endoabs.37.EP698

EP699

Addisonian crisis as a manifestation of a partially empty sella in a 68-year-old woman

Zadalla Mouslech[1], Maria Somali[1], Anastasia-Konstantina Sakali[2], Pavlina Koulara[1], Alexandros Mourouglakis[1], Georgios Tsoutsas[1], Christos Savopoulos[1], George Mastorakos[2] & Apostolos Ioannis Hatzitolios[1]
[1]1st Medical Propedeutic Department of Internal Medicine, AHEPA University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece; [2]Department of Endocrinoloy, Metabolism and Diabetes, Aretaeio Hospital, School of Medicine, University of Athens, Athens, Greece

Introduction
Empty sella syndrome (EES) is a condition often discovered incidentally, where the sella turcica, the structure containing the pituitary gland, appears to be empty.

Patients either remain asymptomatic or, rarely, manifest signs of declined pituitary function. Patients experiencing hypopituitarism are offered hormonal replacement. Autopsy studies estimated a 5% EES prevalence among healthy individuals.
Case report
A 68-year-old post-menopausal woman, overweight (BMI = 29), mother of three children, presented with a 3-day history of fever (T = 38, 5 °C), excessive vomiting and nausea and a history of 15 days of anorexia, weakness and fatigue. Five years ago, during the course of a hospitalization for the investigation of leukopenia, she was diagnosed with myelodysplastic syndrome. Physical examination yielded no pathological findings, whereas laboratory results revealed leukopenia (WBC = 2.900), hypokalaemia (K + 3.2 mmol/l), low TSH levels = 0.18 μIU/ml (n.v. 0.27–4.2), low FT_4 = 6.01 pmol/l, (n.v. 12–22), decreased gonadotropin levels (FSH = 1.3 mIU/ml, n.v. in menopause > 30 and LH = 0.2 mIU/ml, n.v. in menopause > 10), hypocortisolaemia (cortisol = 51 nmol/l,n.v. 171–536 nmol/l) and normal ACTH = 17.3 pg/ml (n.v. 10–60). Adrenal function investigation with the short Synacthen test was positive (cortisol 0 min = 110 nmol/l.30 min = 283 nmol/l, 60 min = 410 nmol/l) and MRI of the pituitary gland demonstrated a partially empty sella turcica, with herniation of the suprasellar cistern. The patient was diagnosed with panhypopituitarism and was initially treated with i.v. administration of methylprednisolone. After discharge, outpatient treatment included levothyroxine and prednisone.
Conclusions
Empty sella may be primary or secondary to surgery, irradiation or infarction of the pituitary gland. Idiopathic ESS usually generates from congenital defects of the sellar diaphragm where arachnoid membrane herniates through the deficient diaphragm, compressing the pituitary gland. In up to 50% of the cases, primary ESS is associated with benign intracranial hypertension. MRI usually demonstrates the compression of the pituitary tissue against the floor of the sella and the subsequent deviation of the pituitary stalk. Hypopituitarism is a rare complication of EES as it manifests when > 90% of the pituitary tissue is compressed or atrophied.

DOI: 10.1530/endoabs.37.EP699

EP700

Fracture of the left wrist as a possible indication of Cushing's disease

Zadalla Mouslech[1], Maria Somali[1], Anastasia-Konstantina Sakali[2], Nikolaos Kakaletsis[1], Georgios Tsoutsas[1], Christos Savopoulos[1], George Mastorakos[2] & Apostolos Ioannis Hatzitolios[1]
[1]1st Medical Propedeutic Department of Internal Medicine, AHEPA University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece; [2]Department of Endocrinoloy, Metabolism and Diabetes, Aretaeio Hospital, School of Medicine, University of Athens, Athens, Greece.

Introduction
Cushing's syndrome is a rare (0.004%) hormonal disorder, which develops due to hypercortisolaemia. Cushing's disease refers to a corticothroph cell pituitary tumour overproducing ACTH, which induces abnormally increased cortisol production from the adrenal glands. Cushing's disease is a causative factor of osteoporosis, hypertension, glucose intolerance and dyslipidaemia.
Case report
A 50-year old woman was referred to our department for the investigation of osteoporosis. She reported a 2-year history of weight gain, hypertension and hair loss and currently a fracture of her left wrist. Reported age of menopause, 49 years. On physical examination her blood pressure was 140/90, she was overweight (BMI = 25) and had bilateral supraclavicular fullness, buffalo hump, calf bruises and white striae on the abdomen. Laboratory examination revealed shortened APTT, eosinopenia, increased fasting glucose, dyslipidemia, high-normal sodium levels (Na + = 145 mmol/l), mild hypokalemia (K + = 3.4), hypercortisolaemia (cortisol = 754 nmol/l, n.v. 171–536), FSH = 132 mIU/ml, LH = 36.9 mIU/ml, ACTH = 136 pg/ml (n.v. 0–60), PTH = 10.8 (n.v. 1.58–6.03) and 24-h urinary free cortisol = 436.4 μg/dl (n.v.10–110). Estimation of lumbar spine bone mineral density by dual-energy X-ray absorptiometry was diagnostic of osteoporosis (T score −3.3). The patient underwent dynamic investigation with dexamethasone-suppressed CRH stimulation (Dex-CRH) test, which indicated ACTH-dependent Cushing's disease. 3 Tesla MRI of the pituitary gland suggested the presence of a microadenoma. Bilateral inferior petrosal sinus sampling (IPSS) established the diagnosis of a microadenoma on the right anterior part of the pituitary gland. Treatment was started with pasireotide 2 × 900 μg daily.
Conclusion
Mortality in Cushing's disease is by eight-times higher than in the general population, especially when the disease is not fully controlled. Unfortunately, many disease-related complications such as hypertension, dyslipidemia and osteoporosis are not completely reversible when diagnosis is delayed. We suggest the diagnosis of Cushing's disease to be considered in the differential diagnosis of osteoporotic fractures or osteoporosis.

DOI: 10.1530/endoabs.37.EP700

EP701

Clinical and molecular differences between invasive and non-invasive pituitary adenomas

David Cano[1], Mariola Mendez-Muros[1], Eva Maria Venegas-Moreno[1], Noelia Gros[1], Elena Dios[1], Natividad Garcia-Hernandez[1], Ainara Madrazo-Atutxa[1], Ignacio Martin[2], Eugenio Cardenas[2], Ariel Kaen[2], Florinda Roldan[3] & Alfonso Soto-Moreno[1]
[1]Endocrinology and Nutrition Unit, Institute of Biomedicine of Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Sevilla, Spain; [2]Neurosurgery Unit, Hospital Universitario Virgen del Rocío, Sevilla, Spain; [3]Radiology Unit, Hospital Universitario Virgen del Rocío, Sevilla, Spain.

Pituitary adenomas are usually benign. However, a significant number of pituitary adenomas show an aggressive behaviour, with local invasion, increased risk of recurrence after surgery and lack of therapeutic response. In this study, we aimed to determine whether invasive and non-invasive pituitary adenomas display differences in clinical features and molecular parameters. In this retrospective descriptive study, 46 pituitary adenomas were analysed. Invasiveness was defined as invasion of surrounding structures like cavernous or sphenoidal sinus on the basis of magnetic resonance imaging and surgical findings. Clinical variables, histological subtype and need for radiotherapy were collected. Quantitative PCR was used to measure the expression of several membrane receptors important for pituitary function: somatostatin receptors (SSTR1–SSTR5), dopamine receptors (DR1-DR5) including the long isoform of dopamine D2 receptor 2, GHRHR, GHSRS1, GHSRS1b, proliferation genes (ki67 and PTTG1) and housekeeping genes (HPRT, GAPDH and β-actin). 30 invasive pituitary adenomas (63.3% non-functioning; 23.3% GH-producing; 13.3% ACTH-producing) and 16 non-invasive adenomas (37.5% non-functioning; 43.8% GH-producing; 18.75% ACTH-producing) were analysed. No significant differences were observed in age and sex between invasive and non-invasive adenomas. Growth of tumour remnants (P < 0,0001) and need for radiotherapy (P = 0.016) was higher in invasive adenomas. Only SSTR3 (P = 0.043), the long isoform of dopamine D2 receptor 2 (P = 0.048) and PTTG1 (P = 0.029) display significant differences between invasive and non-invasive adenomas. SSTR1 (P = 0.007), dopamine D2 receptor (P = 0.019) and PTTG1 (P = 0.039) expression was higher in histological subtypes of aggressive pituitary adenomas. Our preliminary results indicate that invasive pituitary adenomas display differences in clinical features and gene expression. It remains to be determined whether these differences in gene expression might represent a mechanistic link to the invasion process.
Disclosure
This work was supported by Spanish Ministry of Health, ISCIII (grants PI13/02043) and by the Andalusian Regional Ministry of Science and Innovation (CTS-7478).

DOI: 10.1530/endoabs.37.EP701

EP702

Molecular analysis of miRNA expression profiles in AIP mutation positive somatotropinomas

Nikolai Falk[1], Adrian Daly[2], Albert Beckers[1] & Natalia Pellegata[2]
[1]Institute of Pathology, Helmholtz Zentrum München, Munich, Germany, [2]Department of Endocrinology, CHU de Liège, University of Liège, Liège, Belgium.

Germline mutations in the aryl hydrocarbon receptor interacting protein gene (AIP) predispose to pituitary adenomas in young patients, often presenting as familial isolated pituitary adenoma (FIPA) kindreds. Pituitary adenomas in patients with AIP mutations (AIPmut) are usually somatotropinomas, which are more aggressive and have poorer responses to somatostatin analogues than their non-mutated counterparts. Given the rarity of this condition, the molecular pathogenesis of the AIP mutated tumors is still incomplete.
The aim of this study was to determine the microRNA (miRNA) expression profile of AIP mutation-positive somatotropinomas. Tumours from patients carrying AIP mutations (AIPmut; seven tumors from six patients) were compared with somatotropinomas from mutation-negative individuals (AIPwt). RNA was extracted from formalin-fixed, paraffin-embedded tissues. For miRNA profiling, the GeneChip miRNA 1.0 arrays from Affymetrix were used. After filtering for

detection and applying the Benjamini-Hochberg correction of data, a cut-off *P*-value of <0.05 was chosen. This resulted in a total of nine non-coding RNAs significantly differentially expressed between AIPmut and AIPwt adenomas by a fold change $>$ 1.5. Six were up-regulated and three down-regulated in AIPmut *versus* AIPwt tumors. Based on Ingenuity Pathway Analysis, these miRNAs are involved in cell proliferation and motility, cell death and cell cycle. We validated the expression of 5 differentially regulated miRNAs using individual Taqman RT-PCR assays, which allowed us to discount one miRNA. The functions of the differentially regulated miRNAs were assessed in *in vitro* studies, in addition to the role of mutant AIP proteins in regulating miRNAs expression. The identification of biologically relevant miRNAs regulated by AIPmut may give insights into the molecular pathogenesis of AIP-associated somatotropinomas.

Disclosure
This work was supported by Pfizer.
DOI: 10.1530/endoabs.37.EP702

EP703

Mortality in SIADH is similar to that in non-SIADH hyponatraemia; preliminary data

Christopher J Thompson[1], David Slattery[1], Saket Gupta[1], William Tormey[2] & Martin Cuesta Hernandez[1]
[1]Academic Department of Endocrinology, RCSI Medical School, Beaumont Hospital, Dublin, Ireland; [2]Department of Chemical Pathology, RCSI Medical School, Beaumont Hospital, Dublin, Ireland.

Introduction
Excess mortality due to hyponatraemia is well documented but it is not clear whether the mortality associated with SIADH is different to that associated with non-SIADH hyponatraemia (NSH).
Methods/design
Prospective evaluation of all patients admitted with or developing hyponatraemia in a tertiary hospital (pNa $<$130 mmol/l) in January 2015. Diagnosis of SIADH was based on standard clinical and biochemical criteria (pNa, spot urine sodium, urine osmolarity, 0900 h cortisol and TFTs). Statistics were by Mann–Whitney *U*, Student's *t*, or χ^2 tests, as appropriate.
Results (SIADH VS NSH)
180 patients were included. 89 (45 females) were classified as SIADH vs 91 (45 females) as NSH. Clinical data: mean age was similar; SIADH 68 years (S.D.: 15) vs NSH 72 years (S.D.: 15), $P=0.09$. Premorbid history of hypertension, diabetes, COPD, liver disease, and cognitive impairment were similar ($P>0.05$) but CCF (6.7% vs 30.7%, $P<0.0001$) and ischemic heart disease (17.9% vs 31.8%, $P=0.02$) were commoner in NSH. Laboratory data: admission pNa was similar; SIADH 126 mmol/l (S.D.: 5) vs NSH 126 mmol/l (S.D.: 3), $P=0.68$. Other laboratory results (median (IQR), SIADH first): pK: 4 mmol/l (3.6, 4.3) vs 4.1 mmol/l (3.7, 4.9), $P=0.003$. pUrea: 5.3 mmol/l (4, 6.9) vs 11.6 mmol/l (7.4, 18.8), $P<0.0001$, pCreatinine 64 μmol/l (53.5, 74) vs 128 μmol/l (85, 213), $P<0.0001$, and spot uNa: 53.5 mmol/l (32, 89) vs 30 mmol/l (18, 59), $P=0.005$. In SIADH, 0900-h cortisol: 482 nmol/l (IQR: 412, 578), 21% were receiving therapeutic glucocorticoids. One patient with COPD had a subnormal post Synacthen peak cortisol of 363 mmol/l due to recent oral prednisolone course. No patient had hypothyroidism. Duration of hospital admission was similar: SIADH 13 days (11) vs 11 days (10), $P=0.55$ and mortality was similar in SIADH, 5.6% compared to NSH 9.8% ($P=0.34$).
Conclusion
Preliminary results show similar mortality rate in patients with SIADH compared to non-SIADH, although larger number of patients will confirm these observations.

DOI: 10.1530/endoabs.37.EP703

EP704

The higher gastrin levels were associated with better glycaemic control

Georgios Boutzios[1], Krystallenia Alexandraki[1], Panagiotis Moschouris[1], Eleni Lampropoulou[1], Anastasia Evaggelatou[2], Antigoni Velidaki[2], Eufrosyni Kitsou[2] & Gregory Kaltsas[1]
[1]Endocrine Unit, Department of Pathophysiology, Medical School, Laiko Hospital, University of Athens, Athens, Greece; [2]Department of Nuclear Medicine, Laiko University Hospital, Athens, Greece.

Background
Gastrin is an early incretin candidate, since it is released by oral glucose and potentiates the glucose-induced insulin secretion. It has been shown that only in hypoglycaemic or hyperglycaemic conditions gastrin release is influenced by changes in blood glucose and insulin concentrations.
Aim
To evaluate whether there is a relation between fasting serum glucose and serum gastrin concentrations.
Methods
Gastrin and glucose levels and HbA1c were measured in 202 blood samples. We studied gastrin serum concentrations dividing the samples in three subgroups with glucose concentrations $<$100, 101–126, $>$126 mg/dl, and in three subgroups with HbA1c $<$5.7, 5.7–6.4, $>$6.5%, and glucose levels in three subgroups with different gastrin levels 100–200, 200–500, and $>$500 ng/ml.
Results
Gastrin and HbA1c were negatively correlated ($r=-0.27$, $P=0.04$) in the total population of samples studied. No difference was found in gastric concentration in the subgroups of normal, moderately increased, increased glucose concentrations (462.2 ± 311.9, 568.1 ± 164.9, and 387.8 ± 46.2 respectively), or in the subgroups of normal, prediabetic, diabetic range of HbA1c (520.8 ± 285.3, 428.7 ± 327.1, and 297.9 ± 236.5 respectively) but a trend value between normal and diabetic values ($P=0.08$). In low, mid-high, high gastrin levels HbA1c (6.3 ± 9.7, 6.14 ± 0.7, and 5.8 ± 0.6) values but not glucose (109.2 ± 35.9, 111.6 ± 30.6, and 106.2 ± 25.4 respectively) levels different only between low and high gastrin levels ($P<0.001$).
Conclusion
A negative correlation between glucose and gastrin levels has been shown in the present study. In patients with higher gastrin levels, HbA1c was statistically significant lower compared to patients with lower gastrin levels, indicating a better glycaemic control. Nevertheless further studies are needed to confirm these findings.

DOI: 10.1530/endoabs.37.EP704

EP705

Association of polymorphisms of VDR and CASR with clinical and laboratory manifestations of primary hyperparathyroidism

Elena Peretokina[1], Natalia Mokrysheva[1], Lyudmila Rozhinskaya[1] & Ekaterina Zakharova[2]
[1]Endocrinology Research Center, Moscow, Russia; [2]Medical Genetics Research Center, Moscow, Russia.

Clinical manifestations and severity vary considerably primary hyperparathyroidism (PHPT) patients. Several studies indicate that the variation of clinical manifestations PHPT may be associated with genetic factors, in particular the VDR gene polymorphisms and CASR. The purpose of this study was to evaluate the effect of VDR gene polymorphisms and CASR on indicators calcium and phosphorus metabolism, levels of 25(OH)D, PTH, and condition of bone density in patients with PHPT.
Methods
The study involved 187 patients with PGPT (median age 54 (49; 64) years, 160W/27M). The study of polymorphisms CASR (R990G, A986S, and Q1011E). In 166 (139W/27M) patients analyzed polymorphisms VDR – ApaI, Bstm, FokI, Cdx2, and Taq. The distribution of genotypes consistent with the condition of Hardy–Weinberg. All patients were investigated levels of total calcium, ionized calcium, phosphorus in the blood, alkaline phosphatase, calcium in daily urine, PTH, 25(OH)D, and densitometry three parts of the skeleton. 25(OH)D was investigated during the period from November to May.
Result
The analysis of polymorphisms of VDR revealed that polymorphisms FokI and BsmI influence the clinical manifestations PHPT. Carriers of FF genotype polymorphisms FokI level of 25(OH)D was significantly higher than that of genotype ff and Ff ($P=0.014$). In carriers bb genotype polymorphism Bsml level of β-cross laps and osteocalcin was lower than the combined genotype Bb+bb ($P=0.036$ and $P=0.041$) and higher mean values of BMD in the spine ($P=0.038$). Relationship with the calcium levels in the blood, urinary calcium or PTH has been received. There were no associations with different polymorphisms CASR indicators calcium and phosphorus metabolism, PTH, bone turnover markers, BMD in patients with PGPT.
Conclusion
The polymorphisms FokI and BsmI VDR may affect the clinic PGPT that is of interest, given the large variability manifestations PHPT. This result requires further study.

Disclosure
The work was supported by grant of President of Russian Federation Н Ш -4527.2014.7.
DOI: 10.1530/endoabs.37.EP705

EP706

Physiological area of normality of copeptin in normal-to-hyperosmolar states

Ingeborg Schnyder[1], Konrad Strauß[2], Gilbert Koch[3], Carla Walti[4], Marc Pfister[3], Bruno Allolio[2], Wiebke Kristin Fenske[5] & Mirjam Christ-Crain[1]
[1]Universitätsspital Basel, Basel, Switzerland; [2]Universitätsklinikum Würzburg, Würzburg, Germany; [3]Universitäts-Kinderspital beider Basel, Basel, Switzerland; [4]Spital Uster, Uster, Switzerland; [5]Universität Leipzig, Leipzig, Germany.

Background
Copeptin is the C-terminal portion of the precursor of vasopressin. In contrast to vasopressin copeptin is stable *in vitro* and easy to measure. Similar kinetics of both peptides have been described in different trials. However, the physiological area of normality of copeptin has never been evaluated.
Methods
We measured plasma copeptin, sodium, and osmolality levels in 93 healthy volunteers at baseline, during/after i.v. infusion of 3% saline until a sodium level of at least 150 mmol/l was reached, and during/after an oral waterload/i.v. infusion of glucose 5%. In total, 4–19 (median 12) measurements per patient were performed.
Results
Median age of the study participants was 28 years (range 20–54 years) with a balanced gender distribution male/female (46/47). Upon hypertonic saline infusion plasma sodium levels increased from a median of 140 mmol/l (S.D. 2.21) to 152 mmol/l (S.D. 2.44), plasma osmolality from 293 mOsmol/kg (S.D. 6.62.) to 317 mOsmol/kg (S.D. 6.4) and plasma copeptin from 4.1 pmol (S.D. 4.56) to 34.2 pmol/l (S.D. 31.9). The maximal value of copeptin was reached after 150 min (S.D. 28.1), without a time lag to the maximum of plasma sodium or osmolality (reached after 145 (33.9) and 150 (27.4) min respectively). There was a moderate to strong positive correlation between plasma copeptin and plasma sodium ($r=0.58$, $P<0.05$) and plasma copeptin and plasma osmolality ($r=0.48$, $P<0.05$).
Conclusion
There is a correlation between plasma copeptin, plasma sodium, and plasma osmolality levels from normo-to-hyperosmolar states.
Disclosure
SNF Prof. M Christ-Crain, Thermo Fisher Scientific.

DOI: 10.1530/endoabs.37.EP706

EP707

Pancreatic neuroendocrine tumour presenting with malignant hypercalcaemia

Rosa Quilez Toboso, Silvia Aznar Rodriguez & Antonio Hernandez Lopez
Hospital General Albacete, Albacete, Spain.

Introduction
The aim of this report is to present the uncommon clinical presentation of a patient with a pancreatic NET.
Case report
A 55-year-old man with personal history of hypertension, dyslipidaemia, and depression. He was referred to the outpatient for high levels of calcium in repeated assessments during the last year. He referred polyuria and polydipsia. Not clinical history of bone fractures, abdominal pain, or another digestive symptoms. Initial biochemical assessment demonstrated: calcium 11.8 mg/dl (8.5–10.5), phosphate 2.4 mg/dl (2.5–4.5), creatinine 0.68 mg/dl, GGT 121 U/l, FA 182 U/l, PTHi 7 pg/ml (10–65), 25-OH-vit D 8.78 ng/ml (>20), 1,25-OH-vit D 98.8 pg/ml (16–56), ECA 26 U/l (8–52), calciuria 545 mg/day (<400), chromogranin A 152 ng/ml (<100), and rPTH 1.5 pmol/l (<1). Proteinogram and bone scintigraphy negative. Abdominal CT, revealed a 6.6-cm lobular mass at the tail of the pancreas with collateral circulation and multiple focal liver lesions, which occupied 70% of the hepatic parenchyma. Somatostatin receptor scintigraphy exhibited multiple lesions that overexpress somatostatin receptors suggestive of multiple hepatic metastases from neuroendocrine tumor, without pancreatic uptake. Percutaneous FNA (guided by endoscopy) of the pancreatic lesion revealed a well-differentiated NET. Initially, octreotide long-acting release (LAR) 20 mg every 28 days was administrated and calcium levels decreased from 13.7 to 9.4 mg/dl in 3 months. After that, calcium levels increased again so we increased octreotide LAR 30 mg every 28 days, and then every 15 days, but due to biochemical progression everolimus treatment was initiated. After 2 years treatment with SA and 1 year with everolimus there has not been radiological progression. The patient is clinically asymptomatic.
Conclusion
The manifestation of paraneoplastic syndrome due to PTHrP hypersecretion, despite its rareness in NET, should be considered in the differential diagnosis of hypercalcaemia in such tumours.

DOI: 10.1530/endoabs.37.EP707

EP708

The role of adipocytokinic markers in the prognosis of survival and sepsis at critical postsurgical patients

Alexandru Florescu[1,3], Irina Ristescu[2,3], Ioana Grigoras[2,3], Voichita Mogos[1,3] & Dumitru Branisteanu[1,3]
[1]Spitalul Sfantul Spiridon, Iasi, Romania; [2]Institutul Regional de Oncologie, Iasi, Romania; [3]Universitatea de Medicina si Farmacie Gr. T. Popa, Iasi, Romania.

The secretion of adipocytokines is influenced by fat mass, but also by various situations related to acute stress (food deprivation, or critical state related to inflamatory or infectious syndromes). Adipocytokinic secretory profile could be therefore used for the diagnosis of the type of critical state, as well for the evolution and survival prognosis of patients. The modifications of adipocytokinic markers during the first hours after surgical intervention are insufficiently described. We characterised for the first time the precocious dynamics of leptin comparated to classical inflammation markers (C-reactive protein and interleukin 6 (IL6)) during the systemic inflammatory response syndrome (SIRS) or sepsis at patients submitted to surgical intervention. Our prospective study included three groups of 20 patients – the SIRS group (SI) with major elective abdominal surgery, the sepsis group (SE) witn communitary intraabdominal infections and the control group (C). Leptin, C-reactive protein, an IL6 were measured at 0 point in all three groups and then serially for 5 days after surgery. We observed that leptin values increase precociously at 12–24 h in group SI ($P<0.05$), but remain within the normal range in the SE group. The patients from the SE group had a higher survival rate when they had higher leptin (>6 ng/ml) and lower IL6 levels (<150 pg/ml) within the first 24 h. The prognosis was worsened at patients having low leptin and increased IL6 at this time. Leptin has, therefore, a different precocious dynamics in SIRS than in sepsis patients.Early measurement of leptin levels, together with other inflammatory markers, may be useful for the differential diagnosis and prognosis of surgical critical patients.

DOI: 10.1530/endoabs.37.EP708

EP709

Triiodothyronine inhibits TSH secretion through a non-genomic mechanism

Paula Bargi-Souza[1], Francemilson Goulart-Silva[1], Luis M Rendon[2], Tatiana Fioderlisio[2] & Maria Tereza Nunes[1]
[1]Institute of Biomedical Science, University of São Paulo, São Paulo, São Paulo, Brazil; [2]College of Science, Autonomous University of Mexico, City of Mexico, Mexico.

TSH is the main regulator of the thyroid hormones (THs) synthesis/secretion, which in turn exert a negative feedback mechanism on the *Tshb* mRNA expression in the pituitary gland by reducing their transcription rate. Some of triiodothyronine (T_3) effects are also shown in short period of time, characterizing the non genomic actions of THs. It has been shown previously that T_3 acts on posttranscriptional steps of TSH synthesis and reduces its secretion when acutely administered to hypothyroid rats. The present study aimed to: i) characterize the pathways involved in the rapid inhibition of the TSH secretion induced by T_3 in primary cultures of anterior pituitary cells and ii) evaluate the participation of T_3 on calcium and magnesium intracellular mobilization in slices of pituitary of hypothyroid rats. The cultured plates were treated with three different stimuli, RGD (100 μg/ml – 50 min), Wortmannin (1 μM – 30 min), and EGTA (1 mM). Lately, T_3 was added (10^{-8} M) for 30 min. Slices of pituitary were incubated with Fluo-4AM and Magnesium Green AM probes to address the mobilization of calcium and magnesium after T_3 treatment. The results showed a rapid increase of TSHB content in intracellular extracts while the amount of TSH in extracellular media was reduced after T_3 challenge. The treatment with RGD and Wortmannin abolished T_3 effects. No alteration on TSH secretion induced by T_3 was observed in the presence of EGTA in the culture media neither in calcium intracellular

mobilisation, while intracellular concentration of magnesium was altered under the same condition T_3 treatment (16% of pituitary cells). The Therefore, we propose the existence of an additional mechanism that decreases the TSH synthesis/secretion, triggered in few minutes by T_3, through its interaction with αVβ3 integrin at the plasma membrane, featuring a non genomic action of this thyroid hormone on its own synthesis/secretion.

Disclosure
This work was supported by the FAPESP (São Paulo Research Foundation) (2009/17813-9).

DOI: 10.1530/endoabs.37.EP709

EP710

Patient reported outcomes comparing octreotide capsules to somatostatin analogues injections: results from a multicentre, baseline controlled, phase 3 study in acromegaly

Asi Haviv[1], Gary Patou[1] & Susan Mathias[2]
[1]Chiasma Pharmaceuticals, Newton, Massachusetts, USA; [2]Health Outcomes Solutions, Winter Park, Florida, USA.

Background
Somatostatin analogues are the most widely used medical treatment in acromegaly. The available long-acting formulations are administered parenterally (i.m. or deep s.c. injections). Results of a multicentre, baseline controlled, phase 3 study have recently showed that octreotide capsules are an effective and safe treatment in acromegaly. The Treatment Satisfaction Questionnaire for Medication (TQ15M), assessed in the phase 3 study, as exploratory endpoint, compared patient reported outcomes (PRO) in responders to injections vs. responders to oral treatment.
Methods
TQ15M, a validated PRO, consists of 14 multiple choice items encompassing four domains: effectiveness, side effects, convenience, and overall satisfaction. Additional supplemental items were developed specifically for this study and relate to wear-off effects/breakthrough symptoms and direct comparison of the overall satisfaction on octreotide capsules to injections. The results herein include a cohort of 88 patients (of 151 enrolled), who were controlled on oral and continued treatment with octreotide capsules up to 13 months.
Results
More patients reported improvement than deterioration in all domain scores for effectiveness, side effects, convenience, and overall satisfaction (improvement 41, 38, 48, and 39% respectively vs deterioration 28, 13, 39, and 29%, while others maintained their scores). The improved effectiveness score supported the improvement in acromegaly symptoms (AIS score), reported in the phase 3. Mean satisfaction with oral therapy compared to injections based on the direct comparative supplemental question – was 5.2 (scores 0–7), reflecting the answer 'I am satisfied with this medication compared to others' and aligned with 86% of core study completers electing voluntarily to continue into the extension phase.
Conclusions
Patients' satisfaction with octreotide capsules was high. Improvements were noted compared to injections in all TQ15M domain scores, and specifically for effectiveness and side effects. these results correlates with patients electing to continue oral treatment and the improvements noted for acromegaly symptoms.

DOI: 10.1530/endoabs.37.EP710

EP711

Parenteral somatostatin analogues: a focus on injection site adverse reactions

Asi Haviv[1], Susan Kramer[1], Gary Patou[1] & Gary Tillotson[2]
[1]Chiasma Pharmaceuticals, Newton, Massachusetts, USA; [2]Transcrip Partners, Downingtown, Pennsylvania, USA.

Introduction
Injectable somatostatin analogues (SRLs) are the standard medical management of acromegaly. Injection site adverse reactions reported for parenteral SRLs were examined in the literature and in the FDA Adverse Events Reporting System (AERS), and compared to the respective drug labels.
Methods
PubMed was searched using criteria: period 1995–2013, drugs – octreotide (Sandostatin®), lanreotide (Somatuline®), or somatostatin analogues and adverse reactions of interest – e.g. injection site reactions, in treatment of acromegaly and/or carcinoid tumours. FDA AERS files were reviewed for period Q1/2004 to Q1/2014. Adverse events reported in patients treated with somatostatin analogs were extracted as follows: i) drugs – octreotide (Sandostatin®) and lanreotide (Somatuline®), ii) adverse events on which somatostatin analogs were the primary or secondary suspected drug, and iii) preferred terms (MedDRA) containing the keywords: Injection site, Application site and Administration site.
Results
Literature data showed injection site pain in up to 76%, with severe pain in 11%. Other adverse reactions included injection site erythema, hematoma, bruising, edema, induration, nodule formation, pruritus, and lipohypertrophy. In AERS the most frequent injection site adverse reactions reported were injection site mass (85 cases), haemorrhage (74), swelling (41), induration (29), discomfort, erythema, nodule (28 each), and haematoma (26). AERS cases increased annually from ten in 2004 to 434 in 2012 with a total of 858 AEs by case and 2389 AEs by individual report by Q1/2014.
Conclusion
The incidence of injection site adverse reactions in both the literature and the FDA AERS database is higher than that reported in respective somatostatin analog labels and includes AEs of significant concern. Because of the nature of reported injection site AEs and their potential physical burden to patients, an oral alternative to chronic parenteral injections would mitigate these parenteral adverse events and significantly benefit patient care.

DOI: 10.1530/endoabs.37.EP711

Pituitary: clinical

EP712

Sheehan's syndrome: a clinical, biochemical, hormonal, radiological, bone mineral density, and quality of life assessment

Syed Mohd Razi[1], Manish Gutch[1], Sukriti Kumar[2], Abhinav Gupta[1] & Keshav Kumar Gupta[1]
[1]LLRM Medical College, Meerut, Uttar Pradesh, India; [2]SGPGI, Lucknow, Uttar Pradesh, India.

Background
Sheehan's syndrome or *postpartum* pituitary necrosis though rare, is still remains one of the commonest causes of hypopituitarism in the developing parts of world like Indian subcontinent. The clinical presentation is often variable and frequently accompanied by hypogonadism which leads to low bone density due to loss of bone protective effect of oestrogen.
Aims
To find out the bone mineral density and the quality of life (QoL) in patients of Sheehan's syndrome, and to find out the effect of hormonal replacement therapy on outcome.
Material and methods
All patients previously diagnosed as Sheehan's syndrome or newly admitted during the study period of 3 years were enrolled in the study after obtaining an informed consent. Their clinical, biochemical, hormonal, radiological, and bone mineral density (BMD) data were collected. QoL was assessed using the disease-specific QoL both before and after hormone replacement therapy.
Results
Twenty-three patients were enrolled in the study, the mean age of diagnosis was 43.4 ± 14.2 years; mean diagnostic delay was 13.2 ± 7.4 years. Secondary amenorrhoea and lactation failure were the most common clinical presentations. The bone mineral characteristic of patients with Sheehan's syndrome, revels *T*-score, were found to be significantly reduced in lumbar spine (-2.8 ± 0.6) and femoral neck (-2.9 ± 0.8) as also *Z*-score; these are -1.6 ± 0.6 and -1.4 ± 0.6 respectively. Severe osteoporosis (osteoporosis with fracture) was found in three patients (13%), osteoporosis in four patients (17.3%), osteopenia in six patients (26%), and rest ten patients had normal BMD. The QoL of patients with Sheehan's syndrome before and after hormonal replacement therapy for 1 year, before start of therapy the score was 25 ± 8 and it increased to 59.4 ± 8.6 after 1 year of hormonal replacement therapy.
Conclusion
Sheehan's syndrome resulted in multiple pituitary hormone deficiencies in all the patients. Low bone mass and low QoL were frequently seen in patients with Sheehan's syndrome. Both low mineral density ($P < 0.05$) and QoL improved significantly ($P < 0.05$) after hormonal replacement therapy.

DOI: 10.1530/endoabs.37.EP712

EP713

Coexistence of pituitary cyst, ovary dermoid cyst, and mammary fibroadenomas

Evrim Cakir[1] & Aysel Atak[2]
[1]Endocrinology and Metabolism Department, Haseki Training and Research Hospital, Istanbul, Turkey; [2]Family Physician, Haseki Training and Research Hospital, Istanbul, Turkey.

A 17-year-old girl was referred to Endocrinology Unit by her neurosurgeon. She had complained of severe headache, palpation induced galactorrhoea on left mammary and visual abnormalities for 1–2 months. Her menstrual period was regular. On physical examination a pale face and fatigued appearance was noticed. Biochemical and hormonal analyses are as follows: fasting glucose level was 84 mg/dl, serum sodium level was 140 mmol/l (136–145), serum potassium level was 3.9 mmol/l, FSH level was 9.24 mIU/ml, LH level was 13.26 mIU/ml, oestradiol level was 70 pg/ml, prolactin level was 22.14 ng/dl, cortisol level was 16.13 μg/dl, free T_4 level was 0.9 ng/dl, and TSH level was 2.01 mIU/l. Her urine analysis showed a normal density. The laboratory analyses did not reveal any anterior or posterior pituitary deficiencies or excess. She underwent a pelvic and breast evaluation for palpation induced galactorrhoea which has existed the last 6 months. Her pelvic ultrasonography revealed a 2.5 cm hyperechoic mass on her right paraoverian area. Magnetic resonance (MR) evaluation showed a 3.5×4 cm right adnexial mass. Signal characteristic of mass was suggestive of dermoid cyst. Breast ultrasound revealed a 18×11 mm hypoechoic heterogeneous solid lesion. Histopathologic examination of the breast mass was consistent with fibroadenoma. Pituitary MR revealed a $10.8 \times 6.5 \times 7$ mm sellar mass with homogeneous hyperintensity on T1 weight imaging. The mass was localised posteroinferiorly on left pituitary gland. The features of mass was considered to intense cystic adenom or rathke cleft cyst. The coexistence of pituitary cyst, dermoid ovary cyst, and fibrocystic mammary adenoma was seen in the presented case. Patients with cystic lesion in any tissue should be screened for cystic lesions in other compartments of the body and those cystic lesions including solid components should be followed for the functional activation or loss and malign transformation.

DOI: 10.1530/endoabs.37.EP713

EP714

A case of lung cancer with pituitary metastases presented by diabetes insipidus

H Sebila Dokmetas, Hande Ogul Hincal & Ahmet Bilici
Departments of Endocrinology and Oncology, Medical School, Istanbul Medipol University, Istanbul, Turkey.

Cancer metastases on pituitary gland are seen rarely. A 71-year-old male was admitted to Endocrinology Department with polydipsia, polyuria, and diplopia. Urine volume was ~5 l/day. In medical history; he had been diagnosed as having non-small cell lung carcinoma with multiple liver and bone metastases 1 year ago. He took chemotherapies with four cycles of paclitaxel, carboplatin, and zoledronic acid for bone metastases and radiation therapy (RT) was given to L4-S1 vertebras. The size of the lung mass was reduced on the follow-up computed tomography scan; thus, the patient exhibited a partial response. Owing to his complaints like as diabetes insipidus (DI), pituitary MRI was done that showed a sellar and suprasellar mass which occupied infundibulum and the pituitary gland. Older MRI was explored again by us and seen an undiagnosed smaller sellar mass. Also on T1-weighted MRI, the signal intensity was decreased, suggesting the pituitary and infundibulum metastases of current lung cancer. On physical examination; blood pressure was 100/60 mmHg and there was any abnormality. The serum osmolality was 310 mOsm/kg, whereas the urine density was 1005. Laboratory results were GH: 0.098 ng/ml, IGF1: 51.4 μg/l (64–188), TSH: 0.249 IU/ml (0.27–4.2), free T_4: 0.452 ng/dl (0.93–1.7), FSH: 0.492 IU/ml (1.5–12.4), LH: 0.1 IU/ml (1.7–8.6), total testosterone: 0.025 ng/ml (1.93–7.4), ACTH: <1 pg/ml (7.2–63.3), cortisol: 0.755 μg/dl (6.2–19.4), prolactin: 2.71 ng/ml (4.04–15.2), and Na: 143 mEq/l (135–145). Patient started to use desmopressin nasal spray 0.1 mg/ml two puffs per day, prednisolone 5 mg, levothyroxine 25 μg/day for panhypopituitarism and DI. His urine volume was normalized; the polydipsia ceased and his condition becomes clinically better. Also radiation oncology department planned RT for pituitary metastases. When symptoms of DI appear in a patient with lung cancer, pituitary metastases should be considered and evaluated properly, thus, panhypopituitarism is not skipped.

DOI: 10.1530/endoabs.37.EP714

EP715

Evaluation of thyroid nodules in acromegaly

G Gonca Oruk[1], Melike Bedel Koruyucu[2], Husnu Yilmaz[1] & Baris Pamuk[1]
[1]Katip Celebi University Ataturk Training and Research Hospital, Izmir, Turkey; [2]Yildirim Beyazit University Ataturk Training and Research Hospital, Ankara, Turkey.

Nodular thyroid disease is frequently observed in patients with acromegaly. The aim of this study is to evaluate thyroid nodules and thyroid cancer frequency in acromegalic patients. The data of 125 acromegalic (55 males and 70 females) patients followed over 10 years were evaluated retrospectively from the recorded files. Data for gender, age, duration of acromegaly, thyroid function tests, thyroid ultrasonography (US), and thyroid fine needle aspiration biopsy (FNAB) and thyroidectomy pathological specimen results were analysed. The mean age of the patients was 46.9 ± 10.4 years and the mean disease duration was 10 ± 4.8 years. Multinodular goitre was discovered in 66 patients (42.5%), solitary nodule in 11 patients (8.8%), diffuse goitre in three patients (2.4%), and nodule was not detected in 45 patients (36.0%). Nodule size was smaller than 10 mm in 31 patients (40.2%) and larger than 10 mm in 46 patients (59.7%). FNAB was recommended to all of the patients who had nodules larger than 10 mm and whose nodules were smaller than 10 mm and looked suspicious at imaging. FNAB was performed in 35 patients who accepted the procedure and the results were benign in 30 patients, malignant in three patients, atypia of undetermined significance in one patient and suspicious for follicular neoplasm in one patient. Total thyroidectomy was administered to 14 patients and subtotal thyroidectomy to two patients. One thyroid follicular carcinoma and four thyroid papillary carcinomas (4%) were diagnosed and all of the patients received radioactive iodine treatment for ablation of the residual tissue. Thus acromegalic patients should be routinely submitted to thyroid ultrasound evaluation, followed by FNAB of nodules when indicated. Acromegalic patients must be considered as a high-risk group for the development of thyroid cancer and must be closely followed for thyroid nodules and tumours.

DOI: 10.1530/endoabs.37.EP715

EP716

Escape from response to long-term pasireotide treatment in recurrent Cushing's disease

Filip Gabalec[1,3], Petr Husek[2,3], Jaroslav Pacovsky[2,3] & Jan Cap[1,3]
[1]4th Department of Internal Medicine, University Hospital Hradec Kralove, Hradec Kralove, Czech Republic; [2]Department of Urology, University Hospital Hradec Kralove, Hradec Kralove, Czech Republic; [3]Faculty of Medicine in Hradec Kralove, Charles University in Prague, Hradec Kralove, Czech Republic.

Introduction
A transsphenoidal adenectomy (TSFE) is primary treatment of Cushing's disease. Pharmacological management when the disease persists after surgery is a challenge.
Case report
A 47-year-old man was initially diagnosed with CD (petrosal sinus sampling with CRH testing included) after suffering from multiple organ failure in sepsis. Microadenoma 2×4 mm was suspected on the pituitary MRI. Clinical symptoms were markedly improved after first TSFE, but normalisation was not achieved, so he underwent reoperation. No adenoma was present on control MRI, but CD remained active – altered diurnal rhythm, morning cortisol 574 nmol/l, midnight cortisol 555 nmol/l, urinary free cortisol (UFC) 1008 nmol/24 h, altered suppression in suppression tests (111 nmol/l), and ACTH 115 pg/ml. Ketoconazole was no longer available so treatment with cabergoline according to national guidelines was started. Because no effect was observed we started treatment with pasireotide 0.6 mg b.i.d. In 2 months this treatment led to normalization of UFC (208 nmol/24 h), plasma cortisol in normal range, ACTH 49 pg/ml. Mild elevation of HbA1c was observed (from 5.6 to 8.0…6.6…6.3), but diabetes was under control with oral antihyperglycaemic agents. Patient was doing well, reporting better quality of life and physical condition. Unfortunately 16 months after pasireotide introduction he was admitted for diabetes decompensation (glycaemia 37 mmol/l) and bad condition for symptomatic CD (plasma cortisol >2000 mmol/l, ACTH 321 pg/ml, and UFC 12240 nmol/24 h). Pasireotide was discontinued, treatment with insulin was started. For fast deteriorating of his clinical status due to active CD he was indicated to laparoscopic bilateral adrenalectomy as 'ultimum refugium'. The patient is now dispensarised for eventual Nelson's syndrome.

Conclusion
Mild hyperglycaemia at the start of pasireotide is not the reason for discontinuation. According to our best knowledge this is the first case reported of sudden lack of efficacy of pasireotide after long-term effective treatment.
Disclosure
Supported by MH CZ – DRO (UHHK, 00179906) and the programme PRVOUK P37/08.
DOI: 10.1530/endoabs.37.EP716

EP717

Isolated pituitary sarcoidosis stained with a specific MAB against *Propionibacterium acnes*: a case report

Kaoru Yamashita[1], Michita Niiyama[1], Yasufumi Seki[1], Daisuke Watanabe[1], Osamu Isozaki[1], Kosaku Amano[2], Takashi Komori[3], Yoshikazu Okada[2], Yoshinobu Eishi[3] & Atsuhiro Ichihara[1]
[1]Department of Endocrinology and Hypertension, Tokyo Women's Medical University, Tokyo, Japan; [2]Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan; [3]Department of Human Pathology, Tokyo Medical and Dental University Graduate School, Tokyo, Japan.

Introduction
Sarcoidosis is a systemic granulomatous disorder usually affects multiple organs. Approximately 10% of sarcoidosis occurs as isolated neurosarcoidosis in CNS and <10% of neurosarcoidosis develops in a restricted hypothalamic–pituitary area. Recent study has identified *Propionibacterium acnes* in lungs and lymph nodes of many patients with sarcoidosis using a MAB specific for this bacterium (PAB), providing strong evidence for *P. acne* as a pathogen of sarcoidosis (*Modern Pathology*, 2012). We report a case of isolated pituitary sarcoidosis, manifested as an acute onset of secondary adrenocortical insufficiency.
Case
A 29-year-old man suddenly developed severe headache, malaise, and appetite loss 1 year after an extensive skin peeling therapy for pimples. MRI revealed a diffusely and symmetrically enlarged pituitary, protruded upward with a thickened stalk and inhomogeneously enhanced with gadolinium, suggesting anterior hypophysitis. Endocrinologically, baseline ACTH and cortisol was 4.8 pg/ml and 0.4 μg/dl respectively. FT_4 was 0.72 ng/dl, testosterone was 10.3 ng/dl, PRL was 36.1 μg/l, and peak GH response to GHRP2 was 2.3 μg/l. Administration of hydrocortisone improved clinical symptoms and recovered hypogonadism and hypothyroidism by 2 weeks. Blood levels of ACE, lysozyme, and IgG4 were normal. Whole body gallium scanning did not detect any organ involvement other than the pituitary. Pituitary biopsy revealed many non-caseous granulomas accompanied with calcification. Immunostaining with PAB was positive for giant cells and infiltrated mononuclear cells. This patient fulfilled a diagnostic criterion of neurosarcoidosis by clinical manifestation of hypopituitarism, exclusion of other systemic inflammatory disorders, and histological identification of typical sarcoid granulomas.
Conclusion
Isolated pituitary sarcoidosis is an extremely rare inflammatory disorder. Currently six cases were reported and only three of them were biopsy-proven. This is the seventh case of isolated pituitary sarcoidosis and the first case in which *P. acnes* were identified definitely in sarcoid granulomas of the pituitary.
DOI: 10.1530/endoabs.37.EP717

EP718

Pituitary adenoma of aggressive behaviour

Silvia Maraver Selfa, Ana Gómez Pérez, Isabel Mancha Doblas, Isabel María Cornejo Pareja, Maria Molina Vega, Cristina Díaz Perdigones & Francisco Tinahones Madueño
Endocrinology and Nutrition Unity, Virgen de la Victoria Hospital, Malaga, Spain.

Pituitary ACTH-secreting tumour presents with variety of clinical features: normal cortisol secretion and ACTH-immunopositive staining and mild hypercortisolism without typical features of Cushing's disease. We present a 53-year-old male with history of hypertension. First visit (2005): visual loss, bitemporal hemianopsia in campimetry and in MRI pituitary adenoma (2.5 cm) invading cavernous sinus and suprasellar cister. Hormonal study supported panhypopituitarism. After transsphenoidal surgery, there was a tumour rest (9 mm) with left cavernous sinus invasion. Pathology: atypical pituitary adenoma and ACTH-immunopositive staining. There were normal campimetry and persistence of hormonal deficit. In 2006, he received photon radiotherapy (50 Gy) with radiologic stability. After 6 years, left eyelid ptosis (cranial nerves III–VI palsy) appeared. In replacement therapy with hydrocortisone, levothyroxine, and testosterone, presented TSH <0.05 μgUI/ml, FT_4 1.1 ng/dl, prolactin 3.2 ng/ml, testosterone 3.7 ng/ml, cortisol 10 μg/dl, ACTH 53 pg/ml, and IGF1 24 ng/ml. MRI: pituitary solid lesion (1.7 cm) with left cavernous sinus. Transsphenoidal surgery was performed. Ophthalmoplegia persisted. Pathology: pituitary adenoma ACTH-producer, Ki <1%, P53 75%. After surgery: TSH <0.005 μgUI/ml, FT_4 1.2 ng/dl, cortisol 10 μg/dl, and ACTH 64 pg/ml. Hydrocortisone was suspended and an ACTH-test was performed: peak cortisol 14.4 μg/dl. Corticosteroid therapy was maintained. 6 months after surgery: MRI with tumour rest (11 mm) in the left cavernous sinus and right cavernous sinus (16 mm). PET–TC–FDG–metionine: metabolically active injury in both cavernous sinuses. Hormone study: cortisol 17 μg/dl and ACTH 97 pg/ml, so we suspended hydrocortisone. Without treatment cortisol was 16 μg/dl. Nugent test: cortisol 18 μg/dl. FSR (50 Gy) was administered. After 2 months: cortisol 16 μg/dl, ACTH 127 pg/ml, and UFC 320 μg/24 h. We began cabergoline 1 mg/week. The development of Cushing's syndrome in patients with silent corticotropinomas determines a factor of aggressiveness in these tumours. Intensification with cabergoline was performed, and temozolomide was planned in case of progression.
DOI: 10.1530/endoabs.37.EP718

EP719

Somatostatin analogues effectiveness in non-functioning pituitary adenomas in comparison with acromegaly

Jolanta Kunert-Radek[1], Natalia Bozena Zawada[1], Marek Pawlikowski[2], Hanna Pisarek[3] & Maciej Radek[4]
[1]Department of Clinical Endocrinology, Medical University of Lodz, Lodz, Poland; [2]Department of Immunoendocrinology, Medical University of Lodz, Lodz, Poland; [3]Department of Neuroendocrinology, Medical University of Lodz, Lodz, Poland; [4]Department of Neurosurgery and Surgery of Peripheral Nerves, Medical University of Lodz, Lodz, Poland.

Introduction
Somatostatin analogues (SSAs) are used in the treatment of somatotropinomas. Actually, the use of these drugs in clinically non-functioning pituitary adenomas (NFPA) is raised. The aim of the study is to assess the effectiveness of SSA therapy in both groups.
Materials and methods
40 acromegalic patients and 22 patients with NFPA were treated with SSA for the total therapy duration up to 10 years. Hormonal profile, dynamics of tumour size changes, ophthalmic exam with assessement of visual field, somatostatin receptor scintigraphy, immunohistochemistry of somatostatin receptor subtypes of operated tumours as well as patients' quality of life and undesirable effects were analysed.
Results
The significant decrease of GH and IGF1 concentrations was noticed in 95% of acromegalic patients (16 recurrent tumours and 24 primary tumours). The complete normalisation of hormone levels was observed in 57.5% of patients. The evaluation of the tumours' size in MRI revealed their significant decrease in 40% of acromegalic patients including 81% of primary adenomas. The quality of life was improved in almost all patients. Two patients developed cholelithiasis with indication to cholecystectomy. Considering the patients with NFPA the stabilisation of tumour size and visual field was observed in 68% while the reduction of tumour size was noticed in 9% of cases. 23% of patients revealed an increase of adenoma size regarding the reoperation.
Conclusions
SSAs are effective in the treatment of acromegaly. In patients with NFPA the effectiveness of SSA is much lower. However, pharmacotherapy with SSA in the cases of NFPA allows the stabilisation of the disease and can be considered as an alternative for the next neurosurgeries.
DOI: 10.1530/endoabs.37.EP719

EP720

No evidence of impaired oral hormone substitution after gastric bypass surgery in patients with morbid hypothalamic obesity and hypopituitarism secondary to craniopharyngioma

Peter Wolf[1], Yvonne Winhofer[1], Sabina Smajis[1], Renate Kruschitz[1], Karin Schindler[1], Alois Gessl[1], Greisa Vila[1], Wolfgang Raber[1], Felix Langer[2], Gerhard Prager[2], Bernhard Ludvik[3], Anton Luger[1] & Michael Krebs[1]
[1]Division of Endocrinology and Metabolism, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; [2]Department of Surgery, Medical University of Vienna, Vienna, Austria; [3]Division of Endocrinology, Diabetology and Nephrology, Department of Internal Medicine I, Rudolfstiftung, Vienna, Austria.

Background
Craniopharyngiomas (CP) are benign brain tumours presenting in childhood treated by tumour resection together with radiotherapy. In about half of the cured patients hypothalamic damage leading to eating disorders and obesity as well as to hypopituitarism, necessitating consequent hormone substitution therapy, is observed. Bariatric surgery is an efficient treatment strategy for morbid obesity. However, so far it is unknown, whether oral hormone substitution is hampered by impaired intestinal absorption, leading to severe hypopituitarism or adrenal insufficiency.
Methods
Four CP patients with hypopituitarism and morbid obesity treated by gastric bypass surgery were included in this retrospective analysis. Dosage of hormone substitution, hormonal blood concentrations, adverse effects of impaired drug absorption, and anthropometric characteristics were investigated pre and 3–12 months post operatively.
Results
In all CP patients (3W/1M; BMI_{basal} 49 ± 7 kg/m^2) gastric bypass resulted in distinct weight loss (-35 ± 27 kg). In follow-up examinations mean concentration of fT_4 increased ($fT_{4\ basal}$ 0.9 ± 0.31 ng/dl vs $fT_{4\ follow\ up}$ 1.28 ± 0.29 ng/dl). No patient developed any signs of adrenal insufficiency postoperatively. Mean daily dosage of oral thyroid hormone substitution ($levothyroxine_{basal}$ 156 ± 44 µg/day vs $levothyroxine_{follow\ up}$ 150 ± 30 µg/day) and hydrocortisone ($hydrocortisone_{basal}$ 29 ± 12 mg/day vs $hydrocortisone_{follow\ up}$ 26 ± 2 mg/day) was unchanged. Mean IGF1 concentration decreased after weight loss ($IGF1_{basal}$ 217 ± 93 ng/ml vs $IGF1_{follow\ up}$ 111 ± 36 ng/ml), whereas daily growth-hormone substitution was slightly increased ($somatotropin_{basal}$ 0.9 ± 0.5 mg/day vs $somatotropin_{follow\ up}$ 1.0 ± 0.4 mg/day). Minirin dosage and daily fluid intake remained unchanged.
Discussion
Our results in $n=4$ CP patients suffering from hypopituitarism indicate that oral hormone substitution therapy is not impaired following gastric bypass operation, probably making it a safe and considerable treatment strategy in patients suffering from hypothalamic obesity.

DOI: 10.1530/endoabs.37.EP720

EP721

Cabergoline is an effective treatment for clinically non-functioning pituitary adenomas

Yona Greenman[1,2], Odelia Cooper[6], Iris Yaish[1], Eyal Robenshtok[2,5], Nadav Sagiv[1], Tali Jonash-Kimchi[2,4], Jayati Mallick[7], Arkadiusz Gertych[7], Ilan Shimon[2,5], Ram Zvi[2,3], Shlomo Melmed[6] & Naftali Stern[1,2]
[1]Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [3]Department of Neurosurgery, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [4]Neuroradiology Unit, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [5]Institute of Endocrinology and Metabolism, Rabin Medical Center, Petach Tikva, Israel; [6]Pituitary Center, Cedars Sinai Medical Center, Los Angeles, California, USA; [7]Pathology Department, Cedars Sinai Medical Center, Los Angeles, California, USA.

As optimal postoperative management of patients with clinically nonfunctioning pituitary adenomas (NFPA) is a matter of debate, the role of dopamine agonist (DA) therapy in this clinical setting was evaluated.
Methods
Retrospective analysis of prospectively collected data was conducted at two pituitary referral centrer with different standard practices for post-operative management of NFPA: DA therapy or conservative follow up. Dopamine receptor 2 (D2R) expression was examined by immunohistochemistry, D2R long and short isoform mRNA expression was measured by quantitative RT-PCR.
Results
Seventy-nine patients (mean follow-up, 8.8 ± 6.5 years) were treated with DA, either initiated upon detection of residual tumour on postoperative MRI (preventive treatment (PT) group, $n=55$), or when tumour growth was detected during follow-up (remedial treatment (RT) group, $n=24$). The control group received no medication and comprised 60 patients (mean follow-up 6.3 ± 5 years). Tumour mass decreased, remained stable or enlarged respectively in 38.2, 49.1, and 12.7% of patients in the PT group. Shrinkage or stabilization was achieved in 58.4% of the enlarging tumours in the RT group, whereas tumour growth persisted in only 41.6% of them. In contrast, tumour size enlarged in 53.3% and remained stable in 46.7% of subjects in the control group ($P<0.0001$ for all comparisons). 15 years progression-free survival rate was 0.805 for the PT group, 0.48 for the RT group and 0.12 for controls; $P<0.0001$(PT vs control), $P=0.04$ (RT vs control), and $P=0.0053$ (PT vs RT). 41.7% of patients in the control group required additional surgery or radiotherapy as compared to 20.2% of the combined treatment groups ($P=0.0084$). There was no correlation between D2R expression and tumour response to DA treatment.
Conclusions
Dopamine agonist therapy is associated with decreased prevalence of residual tumour enlargement in patients with non-functioning pituitary adenomas, particularly when treatment is instituted prophylactically after surgical resection.
Disclosure
This work was supported by the Israel Endocrine Society (Young Investigator Award), the Doris Factor Endowment Trust, Novartis (Investigator Initiated Award), and the National Center for Advancing Translational Sciences (grant number UL1TR000124).

DOI: 10.1530/endoabs.37.EP721

EP722

A rare adventure of a lymphocytic hypophysitis

Zeynep Canturk[1], Alev Selek[1], Berrin Cetinarslan[1], Ilhan Tarkun[1], Zeynep Akyay[1], Burak Cabuk[2] & Savas Ceylan[2]
[1]Department of Endocrinology and Metabolism, Kocaeli University Faculty of Medicine, Kocaeli, Turkey; [2]Department of Neurosurgery, Kocaeli University Faculty of Medicine, Kocaeli, Turkey.

Introduction
Lymphocytic hypophysitis is a rare endocrine disease involving lymphocytic infiltration and chronic pituitary inflammation. It may result in significant morbidity by loss of pituitary functions and neurological deficits. Pituitary abscess is another rare disease which may be associated with underlying parasellar pathology. Here, we report a case of lymphocytic hypophysitis diagnosed with a pituitary abscess and recurrent suprasellar involvement after surgery.
Case
A 58-year-old female presented with headache, panhypopituitarism and a pituitary lesion with thickening of pituitary stalk. A pituitary surgery was done for definitive diagnosis and it revealed pituitary abscess associated with lymphocytic hypophysitis. Four months after antibiotherapy, the lesion recurred with extension to hypothalamus and compressive symptoms. High dose glucocorticoid treatment was initiated after exclusion of recurrent pituitary abscess with second surgery. The pituitary lesion reduced significantly in 3 months. However, the glucocorticoid treatment had to be stopped earlier due to toxic hepatitis and replaced to azathioprine.
Discussion
Lymphocytic hypophysitis may cause complete loss of vital pituitary functions and neurological deficits. The disease may rarely be complicated with abscess, therefore careful evaluation and surgical treatment should be performed in these cases. Most symptomatic LH require pulse doses of methyl-prednisolone or prednisone followed by a slow taper over a period of weeks to months. Despite good response to these first-line therapies in the majority of patients, relapses are common. In recurrent and symptomatic lymphocytic hypophysitis, high-dose glucocorticoids combined with azathioprine may be a successful choice of treatment.

DOI: 10.1530/endoabs.37.EP722

EP723

Determinants of neutrophil/lymphocyte ratio in acromegaly patients

Merve Yilmaz[1], Arzu Gedik[2], Tevfik Demir[3], Dilek Cimrin[4] & Abdurrahman Comlekci[3]
[1]Endocrinology Department, Samsun Gazi State Hospital, Samsun, Turkey; [2]Endocrinology Department, Agri State Hospital, Agri, Turkey; [3]Endocrinology Department, Dokuz Eylül University Medical Faculty, Izmir, Turkey; [4]Biochemistry Department, Dokuz Eylül University Medical Faculty, Izmir, Turkey.

Introduction
Neutrophil/lymphocyte ratio (NLR) is an indicative of the acute phase response. It is a significant indicator of the systemic inflammation, and considered as a poor prognosis indicator in various disease. We aimed to evaluate NLR and its determinants in acromegaly patients.
Patients and methods
A retrospective chart review of 40 patients with acromegaly and 45 age and sex matched healthy individuals was performed. Patients with active infection, malignancy, chronic inflammatory or autoimmune disease, history of drug use or disease which may affect the hemogram values were excluded from the study. GH, IGF-I and hemogram values of patients were recorded and NLR was calculated. Correlation analysis was performed between GH, IGF-I levels and NLR.
Results
Mean age of the acromegalic patients was 47.68 ± 12.33 and the control group was 45.16 ± 6.83. NLR in acromegalics was 2.04 ± 0.63 and in the control group 1.88 ± 0.70. In terms of NLR, the difference between the two groups was not statistically significant ($P=0.075$). When acromegalics were divided into active ($n=27$) and controlled group ($n=13$) no statistically significant difference was observed between all three groups ($P=0.204$). NLR was 2.08 ± 0.70 in active group and 1.95 ± 0.45 in controlled acromegalics and the difference between the two groups was not statistically significant ($P=0.556$). There wasn't significant correlation between GH, IGF-I levels and NLR. Negative correlation was observed between age and NLR in acromegalics, especially the active acromegalics.
Conclusion
Cardiovascular disease is a major cause of morbidity and mortality in acromegaly patients. Studies reported an association between elevated NLR and increased risk of cardiovascular disease. We didn't found an increase in NLR in acromegalic patients. Also in these patients, there wasn't significant association between GH, IGF-I levels and NLR. However, in the literature we couldn't find any study on this issue. Further studies are required in order to make adequate comment on this topic.

DOI: 10.1530/endoabs.37.EP723

EP724

Serum cortisol in the early postoperative period as predictor of remission in Cushing's disease

Joana Oliveira[1,4], Eva Lau[1,4], Sandra Belo[1,4], Paula Freitas[1,4], Eduardo Vinha[1], Josué Pereira[2], Lígia Castro[3] & Davide Carvalho[1,4]
[1]Endocrinology, Diabetes and Metabolism Department, Centro Hospitalar São João, Porto, Portugal; [2]Neurosurgery Department, Centro Hospitalar São João, Porto, Portugal; [3]Pathological Anatomy Department, Centro Hospitalar São João, Porto, Portugal; [4]Faculty of Medicine of University of Porto, Porto, Portugal.

Introduction
Pituitary surgery is currently considered the preferred treatment for Cushing's disease (CD) and achieves remission in 55–85% of patients. Cortisol falls quickly after surgery, so that early post-operative cortisol level has been used as predictor of remission. There's no agreement about optimal timing for cortisol measurement, with wide variability between centres.
Objective
To assess the value of early post-operative serum cortisol as predictor of remission after pituitary surgery in CD.
Methods
Cross-sectional, retrospective study of patients who underwent pituitary surgery for CD between January/1998 and October/2013. No glucocorticoid replacement therapy was initiated until blood samples were drawn (0800 h the day after surgery).
Results
We evaluated 45 patients, 86.7% (39) female, with a mean age of 38.2 ± 12.9 years at diagnosis. Mean follow-up was 90.4 ± 56.7 months. After surgery, 33 patients (73.3%) achieved cure, 12 patients (26.7%) presented persistent disease. Ten patients relapsed (30.3%), with mean follow-up time until relapse of 64.4 ± 36 months. There were no significant differences in urinary free cortisol, ACTH, serum cortisol and cortisol in the overnight dexamethasone suppression test at diagnosis between patients with and without disease remission after surgery, or between patients with and without disease recurrence. Morning serum cortisol (obtained from 36 patients) the day after surgery was 16.5 ± 18.3 µg/dl, with higher values in patients without cure in comparison with those in remission (27.6 ± 19.3 vs 12.2 ± 16.3; $P=0.043$). Despite this difference, the postoperative serum cortisol was not a good predictor of remission of CD. The value of ACTH 3 months after surgery was not predictive of disease recurrence.
Conclusion
Serum cortisol measured at 24 h after pituitary surgery was not predictive of remission of CD. A longer interval between surgery and hormonal evaluation may allow a more accurate classification of these patients, including those with later remission.

DOI: 10.1530/endoabs.37.EP724

EP725

Predictive factors for remission and recurrence in Cushing's disease: a single-centre study

Joana Oliveira[1,4], Eva Lau[1,4], Sandra Belo[1,4], Paula Freitas[1,4], Eduardo Vinha[1], Josué Pereira[2], Lígia Castro[3] & Davide Carvalho[1,4]
[1]Endocrinology, Diabetes and Metabolism Department, Centro Hospitalar São João, Porto, Portugal; [2]Neurosurgery Department, Centro Hospitalar São João, Porto, Portugal; [3]Pathological Anatomy Department, Centro Hospitalar São João, Porto, Portugal; [4]Faculty of Medicine of University of Porto, Porto, Portugal.

Introduction
Cushing's disease (CD) is characterised by pathologic hypercortisolism caused by an ACTH-secreting pituitary adenoma. The primary modality for definitive treatment is pituitary surgery. The rarity of CD has made it difficult to establish reliable predictive factors of outcomes.
Aim
Assessment of clinical, hormonal, radiological, surgical and histological findings as predictors of remission and relapse of CD.
Methods
Cross-sectional, retrospective study of patients with CD who underwent pituitary surgery between January/1998 and October/2013.
Results
45 patients were evaluated, 39 women (86.7%), with a mean age at diagnosis of 38.2 ± 12.9 years, and a mean follow-up of 90.4 ± 56.7 months. After surgery (1st or 2nd intervention), remission of CD was achieved in 26 patients (57.8%) without recurrence until the last evaluation, and it persisted in nine patients (20%). Ten patients (22.2%) relapsed during follow-up. There were no differences between groups (cured, not cured, with disease recurrence) relating age, gender, presence of preoperative comorbidities (hypertension, diabetes, dyslipidemia and psychiatric disorders), hormonal study at diagnosis, magnetic resonance imaging findings or surgical technique. In eight of 45 patients (17.8%) the histological study did not identify the adenoma. Cured patients presented a higher percentage of positive histology for adenoma, followed by patients with disease relapse and uncured patients (92.3% vs 80% vs 55.6%; $P=0.045$).
Conclusion
The absence of adenoma identification in pituitary histology after surgery was associated with higher risk of persistence or recurrence of CD. Those patients would benefit from a closer follow-up and early evaluation. No other predictive factors were found.

DOI: 10.1530/endoabs.37.EP725

EP726

Effectiveness of somatostatin analogs as first-line or second-line treatment of acromegaly: single centre experience

Agne Abraitiene[1,2] & Vaidotas Urbanavicius[1,2]
[1]Vilnius University Faculty of Medicine, Vilnius, Lithuania; [2]Vinius University Hospital Santariskiu klinikos, Vilnius, Lithuania.

Introduction
The purpose of this study was to evaluate and compare disease outcomes in patients with acromegaly receiving first-line and second-line (after transphenoidal surgery) somatostatin analogs (SSA) treatment.
Methods
The study involved retrospective data collection from charts of 49 patients with acromegaly who were consulted by an endocrinologist in Vilnius University Hospital Santariskiu klinikos between 2007 and 2013.
Results
Patient population consisted of 16 males (32.7%) and 33 (67.3%) females (mean age at diagnosis 54 ± 13 years). Primary SSA therapy was administered in 14 (28.6%) patients who refused or had contraindications to surgical treatment. Transsphenoidal operation was applied as the first-line therapy in 31 (63.3%) patients and led to disease remission in 16 (51.6%) of them. Of surgically treated patients, 15 (48.4%) were diagnosed with desease recurrence and received second-line SSA therapy. Based on the latest GH and IGF-1 results, control and partial control were achieved in 4 (28.6%) and 5 (35.7%) patients in first-line SSA therapy group, and in 7 (46.7%) and 4 (26.7%) patients in second-line SSA therapy group. 5 (35.7%) and 4 (26.7%) of patients in first-line and second-line SSA treatment groups remained uncontrolled. Although we observed higher mean observational period IGF-1 in the first-line SSA treatment group (511.0 (230.9; 791.1) μg/l) as compared to second-line SSA therapy group (403.3 (280.3; 526.2) μg/l), the difference was not statistically significant ($P = 0.384$).
Conclusions
SSAs are more effective in the treatment of acromegaly when applied after transphenoidal surgery, as they help to achieve control of the disease in a greater percentage of patients. Control of the disease remains a challenge despite availability of high-dose SSA treatment as 27–36% of patients receiving primary or second-line SSA treatment remain uncontrolled.

DOI: 10.1530/endoabs.37.EP726

EP727

The impact of diabetes mellitus on the survival of patients with acromegaly

Wen-Ko Chiou[1], Szu-Tah Chen[2], Feng-Hsuan Liu[2], Chen-Nen Chang[2], Ming-Hsu Wang[1] & Jen-Der Lin[2]
[1]Chang Gung University, Taoyuan Hsien, Taiwan; [2]Chang Gung Memorial Hospital, Taoyuan Hsien, Taiwan.

Aims
An increased risk of mortality in patients with uncontrolled acromegaly has been reported in several studies. We aimed to assess the impact of co-morbidities on the survival of patients with acromegaly after long-term treatment and follow-up.
Methods
A retrospective analysis was performed for 285 patients with active acromegaly who were admitted to the Chang Gung Memorial Hospital, Taiwan between 1978 and 2012.
Results
Of these patients, 106 (37.2%) were diagnosed with diabetes mellitus (DM). During the follow-up period, 21 cases of histological proved malignant in acromegalic patients, and DM with acromegaly had a higher incidence of malignancy (13.2% vs 3.8%; $P < 0.01$). The 5-, 10-, and 20-year survival rates were 93.1, 86.9, and 84.7% for the DM group, respectively, and 96.7, 96.7, and 96.7% for the non-DM group, respectively. After a mean follow-up of 15.1 ± 0.6 years, age, DM, coronary heart disease, and malignancy were found to be significant factors of mortality. Control of growth hormone and IGF-1 levels also conferred a marginal survival benefit.
Conclusions
DM and malignancy significantly influence the survival of patients with acromegaly; thus, these patients need close follow-up and appropriate therapy.

DOI: 10.1530/endoabs.37.EP727

EP728

Impact of gsp mutations in somatotroph pituitary adenomas on growth hormone response to somatostatin analogues: a meta-analysis

Zoe A Efstathiadou[1], Alexandra Bargiota[2], Alexandra Chrisoulidou[3], Georgios Kanakis[4], Lamprini Papanastasiou[5], Anastasia Theodoropoulou[6], Stylianos K Tigas[7], Dimitra Vassiliadi[8], Maria Alevizaki[9] & Stylianos Tsagarakis[10]
[1]Department of Endocrinology, 'Hippokration' General Hospital of Thessaloniki, Thessaloniki, Greece; [2]Department of Endocrinology, University of Thessaly, Larissa, Greece; [3]Department of Endocrinology-Endocrine Oncology, Theagenion Cancer Hospital, Thessaloniki, Greece; [4]Endocrine Unit, Athens Naval and VA General Hospital, Athens, Greece; [5]Department of Endocrinology and Diabetes Center, Athens General Hospital 'G. Gennimatas', Athens, Greece; [6]Department of Internal Medicine, Division of Endocrinology, University Hospital of Patras, Rio, Greece; [7]Department of Endocrinology, University of Ioannina, Ioannina, Greece; [8]Endocrine Unit, Second Department of Internal Medicine, University of Athens, Medical School, 'Attikon' Hospital, Athens, Greece; [9]Endocrine Unit, Department of Medical Therapeutics, Athens University School of Medicine, Athens, Greece; [10]Department of Endocrinology, Evangelismos Hospital, Athens, Greece.

Objective
Somatic mutations in the GNAS1 gene, which encodes the alpha-subunit of G stimulatory proteins (gsp), are frequently detected in somatotroph pituitary tumors and have been associated to specific clinical-smaller and less invasive tumors occurring in older patients- and histopathological-densely granulated adenomas- characteristics. However, the question whether the presence of a somatic gsp mutation affects the response to somatostatin analogue treatment remains unresolved.
Design
Following a literature search, we performed a meta-analysis, including eight eligible studies, in order to estimate the effect of gsp mutation on the percent reduction of growth hormone (GH) levels during an acute octreotide suppression test (OST). A total of 310 patients with acromegaly (126 gsp (+) and 184 gsp (−)) were included in the analysis.
Results
The presence of the gsp mutation was related with a greater reduction in GH levels on OST (weighted mean difference (WMD): 9.08% (95% CI, 2.73, 15.42; $P = 0.005$; random effects model). There was significant heterogeneity for this effect estimate ($I^2 = 58\%$, P value for heterogeneity = 0.02). A sensitivity analysis after exclusion of a study with different methodology of OST provided similar estimates (WMD: 6.93% (95% CI, 1.40, 12.46); $P = 0.01$) albeit with no significant heterogeneity ($I^2 = 35\%$, P value for heterogeneity = 0.16).
Conclusions
The present meta-analysis suggests a role for gsp mutation as a predictive factor of which patients with acromegaly are best candidates for treatment with somatostatin analogs. In order to further clarify this position, studies evaluating the long term effect of treatment, using the combination of GH and IGF-1 measurements are needed.
Disclosure
The Greek School of Endocrinology Initiative was organized and funded by Ipsen. Statistical support and publication costs associated with this paper were also funded by Ipsen. The development at all stages of the concept and content of this pa

DOI: 10.1530/endoabs.37.EP728

EP729

Does cigarette smoking affect serum total cortisol and salivary cortisol levels?

Gulsah Elbuken, Zuleyha Karaca, Fatih Tanriverdi, Kursad Unluhizarci, Yasin Simsek & Fahrettin Kelestimur
Department of Endocrinology and Metabolism, Erciyes University, Medical School, Kayseri, Turkey.

Aim
Although there are some studies regarding the effects of cigarette smoking on serum total cortisol (STC) and salivary cortisol (SaC) levels, the results are still challenging. For this purpose, we aimed to determine the effects of cigarette smoking on STC and/ or SaC levels in a small group of healthy volunteers.
Study design
15 (five female and ten male) cigarette smoker with the mean age of 39.47 ± 14.27, and 15 age and gender matched non-smoker (mean age: 42.47 ± 13.46)

healthy people recruited to the study. Hypothalamo-pituitary-adrenal (HPA) axis was evaluated by basal STC and SaC levels, and STC and SaC responses to standard dose (250 μg) ACTH stimulation test. STC and SaC levels were obtained basal and stimulated conditions.
Results
Basal STC levels were statistically lower in smokers than non-smokers (8.41 ± 4.52 and 13.36 ± 6.68 μg/dl, respectively). Although peak STC were lower in smoker male group than non-smoker male group (30.41 ± 5.79 and 41.10 ± 12.87 μg/dl, respectively), SaC levels were not different (2.41 ± 0.31 and 2.16 ± 1.00 μg/dl, respectively). SaC levels were not affected by cigarette smoking in overall group or in the sub-groups of gender, either.
Conclusion
In our study, SaC levels were not found to be different in smoker group than non-smokers. Further studies including more subjects are needed.

DOI: 10.1530/endoabs.37.EP729

EP730

Evaluation of long term soccer playing caused growth hormone deficiency: a pilot study

Gábor László Kovács[1], Piroska Turbucz[1], Éva Rimanóczy[2], Gergely Pánics[3], Katalin Bánáti[1] & Miklós Góth[4]
[1]1st Department Internal Medicine Flor Ferenc Hospital, Kistarcsa, Hungary; [2]Department of Laboratory Heim Pal Pediatric Hospital, Budapest, Hungary; [3]Department of Orthopedics and Traumatology Uzsoki Hospital, Budapest, Hungary; [4]2nd Department of Internal Medicine, Medical Centre, Hungarian Defence Forces, Budapest, Hungary.

Objective
Our aim was to evaluate whether multiple mild head trauma or repetitive heading of long term soccer playing causes growth hormone deficiency.
Patients and methods
28 retired previously professional male soccer players were investigated. Nine of them had sport related head injuries. Mean age: 48.7 years (range 36–70; S.D. ± 7.4); mean sport duration (professional and senior activity): 27.4 years (S.D. ± 8.17). IGF-I, luteinizing hormone (LH), total testosterone (TT) and quality of life with the QoL-Assessment of Growth Hormone Deficiency in Adults (AGHDA) questionnaire were investigated.
Results
The mean IGF-I was 376.87 ng/ml (range 214.30–503.26 ng/ml S.D. ± 81.42), the mean IGF-I-S.D. score (SDS) value was 2.19 (range 0.74–3.02). The mean LH was 4.12 IU/l (S.D. ± 1.25; normal range: 0.57–12.07), mean TT was 17.44 nmol/l (S.D. ± 7.03; normal range 5.76–30,4). The mean QoL – AGHDA score showed normal value 2.4 points (range 0–12 S.D. ± 3.4), but only four of the subjects had more, than five scores (normal <6). No significant differences ($P>0.05$ in all cases) were found between players with or without head injuries in IGF-1 (385.99 ng/ml ± 85.9 vs 368.41 ng/ml ± 81.21), in IGF-I-SDS (2.23 vs 2.13), in LH (3.36 ± 1.08 vs 4.42 ± 1.19), in TT (16.64 nmol/l ± 7.94 vs 17.92 nmol/l ± 6.59) and in QoL-AGHDA scores (3.22 ± 3.76 vs 2.05 ± 3.23).
Conclusions
There was no difference between normal populations and retired soccer players in IGF-I SDS values, LH, TT levels and QoL-AGHDA scores. The results suggest that long term soccer playing does not damage the most vulnerable pituitary hormone secretion. Although the dynamic tests (e.g. insulin tolerance test) in a larger population would result more reliable data, but according to our pilot study the consequence of these dynamic investigations are ambiguous.
Disclosure
IPSEN Pharma Hungary, Novo Nordisk Hungary

DOI: 10.1530/endoabs.37.EP730

EP731

Carney complex – a case report

Helena Urbánková, Michal Kulich, Elena Vetešková & Peter Vanuga
National Institute of Endocrinology and Diabetology, Lubochna, Slovakia.

Carney complex (CNC) is rare autosomal dominant disorder, which was firstly described as a combination of manifestation of myxomas, spotty skin pigmentation and endocrine overactivity in 1985. This condition affects many organs and varies in clinical manifestation. The presence of at least two clinical signs is considered as pathognomonic with regard to a sporadic form of CNC, and an evidence of at least one sign with simultaneous manifestation of CNC in any of first degree relatives is considered as pathognomonic with regard to a familiar form. Intracardiac and extracardiac myxomas are the most common diagnostic signs. In our report, we present a case of 36-year male patient with history of surgery for testicular Sertoli – cell tumour and surgery of thyroid nodule, with diagnosis of acromegaly. The patient was examined for persistence of hypersomatotropism after partial resection of growth hormone secreting pituitary adenoma, followed by radiation treatment with Leksell γ knife and treated by somatostatin analogues. Recently, as a part of differential diagnosis procedure aiming to discover other increased endocrine activity, we consider potential occurrence of intermittent hypercortisolism based on primary pigmented nodular adrenocortical disease. As a part of comprehensive examination of associated complications of acromegaly we added echocardiography with findings of intracardiac tumours. Drifting thrombus, or bacterial flora, or myxomas were considered as options in differential diagnosis. Patient underwent urgent surgical excision of myxomas in left and right atrium at Cardiac Surgery Clinic. The diagnosis of Carney complex was confirmed by genetic testing.

DOI: 10.1530/endoabs.37.EP731

EP732

Efficacy and safety of tolvaptan in treatment of SIADH; case-series from 2 UK hospitals

Ploutarchos Tzoulis[1], Julian Waung[2], Bernard Khoo[1], Mark Cohen[2] & Pierre-Marc Bouloux[1]
[1]Royal Free Hospital/UCL Medical School, Centre for Neuroendocrinology, London, UK; [2]Barnet Hospital, London, UK.

Introduction
Contrary to US guidelines, recent European guidelines do not recommend tolvaptan for the treatment of SIADH.
Methods
Retrospective data collection of all inpatients treated with tolvaptan for SIADH in two UK hospitals between November 2010 and February 2014. All values were calculated as mean ± S.D.
Results
This case series included 61 patients (33 females, 28 males) aged 74.4 ± 15.3 years with serum sodium (sNa) 119.9 ± 5.5 mmol/l. The aetiology of SIADH was malignancy (24.6%), unknown (24.6%), pulmonary (14.7%), neurosurgical (11.5%), drug-induced (9.8%), post-operative (9.8%) and various (5%). Initiation tolvaptan dose was 15 mg in 55/61 and 7.5 mg in 6/61 cases. 24 h after administration of tolvaptan, sNa increased by 9 ± 3.9 mmol/l; specifically, 2–8 mmol/l in 45.9%, 9–10 mmol/l in 16.4%, 11–12 mmol/l in 19.7% and >12 mmol/l in 18% of patients. Overcorrection, defined as sNa increase of >12 mmol/l in 24 h or >18 mmol/l in 48 h, was observed in 22.3%, while increase of >10 mmol/l in 24 h occurred in 39.3% of patients. No patients developed osmotic demyelination syndrome. None of 12 patients with baseline sNa $\geqq 125$ mmol/l exhibited increase >10 mmol/l in 24 h. The duration of tolvaptan use was 4.2 ± 4 days. At the end of tolvaptan therapy, sNa increased by 13.5 ± 5.9 mmol/l with only 2/61 (3.3%) 'non-responders', having sNa increase ≤ 5 mmol/l or sNa ≤ 130 mmol/l.
Five days after withdrawal of tolvaptan, mean change of sNa was −3.8 ± 6.6 mmol/l with sNa reduction by $\geqq 5$ mmol/l in 21/50 (42%) patients.
Conclusions
Tolvaptan is effective, but can often lead to overcorrection of hyponatraemia. Physicians should monitor closely sodium levels and take appropriate measures to prevent or reverse overcorrection, especially in patients with baseline sNa ≤ 125 mmol/l.

DOI: 10.1530/endoabs.37.EP732

EP733

Evaluation of GH secretion after stroke

Orsolya Nemes[1], Zita Tarjanyi[1], Laszlo Szapary[2], Beata Ruzsa[1], Beata Bodis[1], Laszlo Bajnok[1] & Emese Mezosi[1]
[1]1st Department of Internal Medicine, University of Pecs, Pecs, Hungary; [2]Department of Neurology, University of Pecs, Pecs, Hungary.

Objective
According to recent studies, impaired secretion of GH is a frequent finding after ischaemic stroke. The aim of our study was to compare various available GH stimulation tests in post-stroke patients.
Design
Seventeen patients were included in the study (12 males; mean age: 60.5 years; mean BMI, 27.7 kg/m^2) with a mean 19.6 ($\pm$7.3) months after stroke. For screening, glucagon and small dose (0.15 μg/kg) GHRH-arginine (sdGHRH-A) stimulation tests were carried out in consecutive days. If either or both of them were abnormal, a large dose (1 μg/kg) GHRH-arginine (ldGHRH-A) stimulation, as a standard confirmatory test was carried out, as well.
Results
Maximum GH values reached in sdGHRH-A and glucagon stimulation tests were strongly correlated to each other ($r=0.943$; $P<0.001$), but neither showed association with ldGHRH-A results. Furthermore, IGF-I levels did not correlate with stimulated peak GH values received in any of the three tests. Comparing diagnostic interpretations of stimulation tests to each other, considerable discrepancies were detected in all directions, partly due to various cut-off values of the applicable criteria.
Conclusions
Abnormal GH secretion is common after stroke. If this indication were being included in the screening for GH insufficiency, a larger trial is warranted to evaluate which tests are appropriate because a single GH stimulation test may not necessarily be enough in this population.

DOI: 10.1530/endoabs.37.EP733

EP734

Association of serum IGF1 concentration with efficacy and safety measures in adults with GH deficiency with different GH treatment regimes: a randomised clinical trial

Christa C. van Bunderen[1], Paul Lips[1], Mark H. Kramer[2] & Madeleine L. Drent[1]
[1]Department of Internal Medicine, Section Endocrinology, VU University Medical Center, Amsterdam, The Netherlands; [2]Department of Internal Medicine, VU University Medical Center, Amsterdam, The Netherlands.

Introduction
The current guidelines state that the goals of growth hormone (GH) therapy should be an appropriate clinical response and avoidance of side effects. The target level for IGF1 is commonly the upper half of the reference range, although no published studies offer specific guidance in this regard. Therefore, the aim of the present study is to investigate associations between IGF1 levels within the reference range and several efficacy and safety measures of GH treatment in substituted GH deficient adults.
Methods
32 subjects receiving GH therapy for at least a year with a stable IGF1 concentration of -1 to 1 S.D. score (SDS) were included and randomized to receive either a decrease of their regular dose (IGF1 target level of -2 to -1 SDS) or an increase of their dose (IGF1 target level of 1–2 SDS) for a period of 6 months. Measurements of body composition, lipid profile, glucose metabolism, physical performance and quality of life, next to information on tolerability were collected.
Results
Thirty subjects (65.6% male, mean age 46.6 (9.9 S.D.) years) could be analysed. Decreasing the GH dose lead to more experienced fatigue. Increasing the GH dose lead to an improvement of the walking distance (6-min walking test: change 25.5 (29.7 S.D.) meters, $P=0.01$), and to an overall better feeling ($P=0.04$). There was a trend of a difference in change between de- and increasing GH dose in waist circumference ($P=0.07$) in favour of increasing dose. However, increasing GH dose resulted in a higher fasting glucose (0.4 (0.7 S.D.) mmol/l, $P=0.05$) and subjects experienced more myalgia.
Conclusion
Although increasing GH dose to IGF1 levels of 1 to 2 SDS improved physical performance and subjects reported an overall better feeling, safety is not guaranteed with the demonstrated effect on glucose metabolism and reported adverse events.
Disclosure
This work was partly supported by an investigator-initiated grant from Pfizer bv. C C van Bunderen is supported by an AGIKO grant of The Netherlands Organisation for Health Research and Development (ZonMw) (grant number: 92003591).

DOI: 10.1530/endoabs.37.EP734

EP735

Aetiology of hypopituitarism in adult life: last 10 years' experience in single centre database in Serbian population

Mirjana Doknic[1,2], Sandra Pekic[1,2], Dragana Miljic[1,2], Marko Stojanovic[1], Vera Popovic[1,2] & Milan Petakov[1,2]
[1]Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Centre of Serbia, Belgrade, Serbia; [2]School of Medicine, University of Belgrade, Belgrade, Serbia.

Hypopituitarism as deficiency of one or more anterior pituitary hormones, in adults can be consequence of acquired or genetic causes. Only few published studies investigated population-based aetiology of hypopituitarism. In the last 10 years new risks for hypopituitarism have been recognised (traumatic brain injury-TBI, subarachnoid haemorrhage, cranial irradiation).
Aim
To present our experiences in the aetiology of hypopituitarism based on data collected during last 10 years in Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Centre of Serbia. This is a single centre cross-sectional database study.
Patients
A total of 426 patients with hypopituitarism were included, mean age 44.6$\pm$0.8 years (range 16–82), male 60.3%.The mean age at diagnosis of hypopituitarism was 37.7$\pm$1.2 years. Inclusion criteria were: patients older than 16 years, hypopititarism confirmed by endocrine assessment of pituitary function and MRI of the sellar region. Results are expressed as mean$\pm$SE and percentages (%). Adult onset of hypopituitarism (AOGHD) is reported in 73% pts, while childhood onset of hypopituitarism (COGHD) in 27% pts.
Results
The most common causes of hypopituitarism are: nonfunctional pituitary adenoma (160 pts, 37.6%), followed by congenital causes (66 pts, 15.5%). Acromegaly and prolactinomas are present in 30 pts (7.0%) each, followed by craniopharyngiomas (28 pts, 6.6%). TBI was the cause of hypopituitarism in 19 pts, (4.5%). Other aetiologies are reported in less than 4% in each category. Gonadotroph (FSH/LH) and growth hormone (GH) deficiency are the most common pituitary hormone deficiencies (71% and 70.3% respectively) followed by TSH (69%) and ACTH (69%) deficiency.
Conclusion
Our results show that aetiology of hypopituitarism may depend on the period of time study. Our transition clinic with paediatric endocrinologists in the last years influenced high prevalence of congenital hypopituitarism. Similarly our database confirms that patients with brain damage either by traumatic brain injury or cranial irradiation are at high risk for hypopituitarism.
Disclosure
This work was supported by the Serbian Ministry of Science (project number 175033).

DOI: 10.1530/endoabs.37.EP735

EP736

Persistent hyponatremia in patient with acromegaly, congestive heart failure and diabetes insipidus

Maria Kurowska, Joanna Malicka, Agnieszka Zwolak & Jerzy S Tarach
Department of Endocrinology, Medical University, Lublin, Poland.

Introduction
Increased production of vasopressin plays a key role in the development of fluid retention and hyponatremia in patients with decompensated heart failure. Antidiuretic hormone deficiency in the course of diabetes insipidus leads to the loss of water, dehydration and hypernatremia. The aim of the study was to present difficulties in successful treatment of hyponatremia in a patient with cardiomyopathy and heart failure, receiving desmopressin because of post-operative diabetes insipidus.
Case report
70-year-old man with somatic features of acromegaly, after transsphenoidal surgery propter pituitary microadenoma (7.2 mm). Postoperative histopathological examination showed pituitary adenoma, ACTH ($-$); TSH ($-$); FSH ($+$); PRL ($+$), HGH ($+$). He developed postsurgical pituitary insufficiency requiring long-term substitution of hydrocortisone, thyroxin, testosterone and desmopressin. Before the diagnosis of acromegaly, the clinical picture was dominated by symptoms of cardiomyopathy. After surgery there was an improvement of heart failure, lasting for about 8 years. 4 years ago the worsening of heart failure

appeared with an increased atrial natriuretic peptide ranging from 701–2358 pg/ml. Between 2010–2011 the patient was hospitalised eight times in cardiological and endocrinological departments because of circulatory decompensation and severe hyponatremia (118–120 mmol/l). Dilated cardiomyopathy was diagnosed with insufficiency of mitral valve III°, tricuspid valve III°, aortic valve II° and congestive heart failure NYHA II/III. Substitution of adrenal and thyroid insufficiency was correct. In October 2011, after a withdrawal of desmopressin, normalisation of sodium levels and improvement of heart function persisting up to now were achieved.
Conclusion
An improvement of heart failure and normalization of blood natremia after the desmopressin withdrawal may suggest the regression of diabetes insipidus in our patient (9 years after an operation?), or, what is more likely, the beneficial influence of partial deficiency of antidiuretic hormone on reduction of the retention of body fluids and cardiovascular efficiency.

DOI: 10.1530/endoabs.37.EP736

EP737

Clinical features of pituitary adenomas in elderly patients in Castilla La Mancha (Spain) compared with younger age group; a retrospective multicentre study

Almudena Vicente[1], Florentino Del Val[1], Claudia Cortés[1], Cristina Lamas[2], Miguel Aguirre[3], Julia Silva[4], Moubarak Alramadán[5] & Iván Quiroga[6]
[1]Department of Endocrinology and Nutrition, Hospital Virgen de la Salud, Toledo, Spain; [2]Department of Endocrinology and Nutrition, Hospital General Universitario, Albacete, Spain; [3]Department of Endocrinology and Nutrition, Hospital General Universitario, Ciudad Real, Spain; [4]Department of Endocrinology and Nutrition, Hospital General La Mancha-Centro, Ciudad Real, Spain; [5]Department of Endocrinology, Hospital Virgen de la Luz, Cuenca, Spain; [6]Deparment of Endocrinology, Hospital Nuestra Señora del Prado, Talavera, Spain.

Background
Pituitary adenomas (PAs) in the elderly, defined as people older than 65 years, represent less than 10% of all PAs. Because of increasing life expectancy and improving health care, diagnosis PAs in this age group is increasing with time. Age-related changes and associated diseases may significantly modify the clinical presentation in these patients, delaying the diagnosis of PAs.
Objective
To analyse the clinical features of PAs in elderly patients in a study population from Castilla – La Mancha (Spain).
Design
Retrospective observational study.
Methods
The study included 346 patients with a presumptive diagnosis of pituitary adenoma between 2000 and 2012. Review of medical records of elderly patients with PAs was carried out.
Results
67 patients, 19.4% of whole PAs, were studied (62.7% women). Mean age was 73 years (range 65–87). At presentation, visual impairment, headache and deficiency of $\geqq 1$ pituitary axes were detected respectively in 43.3, 47.6 and 50.8% of the patients with available data. There were statisti-cally significant differences in visual impairment (43.3% vs 16.3%, $P<0.001$), deficiency of $\geqq 1$ pituitary axes (50.8% vs 30.5%, $P<0.001$), incidental diagnosis (47.8% vs 14.9%, $P<0.001$) or pituitary apoplexy (10,4% vs 1%, $P<0.001$) between elderly and younger patients at presentation. 59 (88,1%) out of 67 patients had macroadenomas whereas 8 (11.9%) had microadenomas. Mean size of PAs in elderly patients was significantly greater than non elderly patients ($23.9 \pm 12 \pm 0$ mm vs 15.2 ± 12.4 mm, $P<0.001$). 58 (86.8%) were non-functioning pituitary adenomas, 3 (4.5%) prolactinomas, and 6 (8.9%) GH-secreting adenoma. There was none ACTH – secreting adenoma.
Conclusions
The proportion of elderly patients in our study is higher than in other studies. Our data show that there are age-related differences in PAs clinical features at diagnosis. Visual impairment, hypopituitarism, incidental diagnosis, pituitary apoplexy and larger size are more frecuent features in elderly patients than in their younger counterparts. Most of PAs in elderly patients are macroadenomas and clinically non-functioning.

DOI: 10.1530/endoabs.37.EP737

EP738

Obstructive sleep apnoea is common in patients who have had surgery for non-functioning pituitary adenomas; preliminary data

Martin Cuesta Hernandez[1], Rachel Crowley[1], Richard Costello[2] & Christopher Thompson[1]
[1]Academic Department of Endocrinology, Beaumont Hospital, Dublin, Ireland; [2]Academic Department of Pulmonology, Dublin, Ireland.

Introduction
Some patients complain of excessive daytime somnolence following pituitary surgery.
Aim
To investigate the presence of obstructive sleep apnoea (OSA) following surgery for non functioning pituitary adenomas (NFPA).
Design and methods
We assessed the prevalence of OSA in 16 routinely selected patients following surgery for NFPA and 13 obese controls attending a tertiary referral centre, by means of the Epworth Sleepiness Score (ESS) and polysomnography. All subjects with sleep apnoea were offered continuous positive airway pressure therapy (CPAP).
Results
The median age in NFPA group was 60 years (IQR: 51, 67) vs 49 years (IQR: 43, 56), $p=0.023$. Gender: Male: 9/16 (56%) in NFPA vs 7/13(53%) in control group, $P=0.89$. 15/16 (93%) patients had postoperative hypopituitarism and were on appropriate hormone replacement at the time of evaluation Median ESS was 13 (IQR: 5.25, 36) in NFPA patients and 5.7 (1.75, 18.55) in controls, $P=0.04$. 14 (87%) NFPA patients had apnoea hypopnoea index (AHI)>5, compared to seven patients (53%) in the obese control group, $P=0.043$, with 10/15 (66%) with complete anterior pituitary failure. 9/10 (90%) patients with complete anterior pituitary failure were diagnosed from OSA (AHI>5) and were started on CPAP. There were no statistically significant differences in the prevalence of OSA in patients with complete anterior pituitary failure after surgery (90%) compared to those with partial anterior hypopituitarism 4/6 (66%), $P=0.24$. BMI did not correlate with apnoea hypopnoea index (apnoea – hypopnoea index (AHI), $r=-0.17$, $P=0.54$), which suggests that factors other than obesity might explain the prevalence of sleep apnoea after surgery in patients with NFPA.
Conclusions
OSA is common following surgery for NFPA, and is not explainable solely by associated obesity. Polysomnography should be offered to NFPA patients with somnolence or symptoms of OSA.

DOI: 10.1530/endoabs.37.EP738

EP739

Mean platelet volume in patients with prolactinoma

Abbas Ali Tam[1], Cafer Kaya[1], Reyhan Ersoy[2] & Bekir Çakır[1]
[1]Department of Endocrinology and Metabolism, Ataturk Training and Research Hospital, Ankara, Turkey; [2]Department of Endocrinology and Metabolism, Yıldırım Beyazıt University, Ankara, Turkey.

Introduction
Prolactin is a multifunctional pituitary hormone. The effect of prolactin on platelet activation is not well understood. Prolactinomas are the most common type of pituitary adenomas, and they are medically responsive to dopamine agonists. Mean platelet volume (MPV) is a marker of platelet function and activation. The aim of this study was to evaluate MPV values before and 6 months of cabergoline treatment when normoprolactinemia was achieved.
Methods
A total of 101 newly diagnosed prolactinoma patients and 102 healthy control subjects were included in the study. Patients with haematological disorders that affect MPV and those on medications were excluded. Prolactin, platelet count and MPV levels were recorded before and 6 months after the initiation of cabergoline treatment (0.5–1 mg, two times a week).
Results
There was no significant difference in platelet count and MPV before and after 6 months of treatment with cabergoline in patients with prolactinoma compared with the control group ($P>0.05$).
Conclusion
Our results showed that MPV, a marker of platelet function, was unchanged in patients with prolactinoma.

DOI: 10.1530/endoabs.37.EP739

EP740

Differentiated thyroid cancer in patients with prolactinoma

Abbas Ali Tam[1], Cafer Kaya[1], Cevdet Aydın[1], Reyhan Ersoy[2] & Bekir Çakır[2]
[1]Department of Endocrinology and Metabolism, Ataturk Training and Research Hospital, Ankara, Turkey; [2]Department of Endocrinology and Metabolism, Yıldırım Beyazıt University, Ankara, Turkey.

Introduction
Increasing evidence is available for the role of prolactin in the development of various cancers. The purpose of this study is to evaluate the frequency of thyroid cancer in patients with prolactinoma followed up at a single site.
Materials and methods
Medical records of 182 patients, diagnosed with prolactinoma, were reviewed retrospectively. Out of these patients, 114 patients (103 female patients, 11 male patients, mean age 35 ± 10.4), who had undergone thyroid ultrasonography (US), were included in the study. Serum prolactin, anti-thyroglobulin (antiTg), anti-thyroid peroxidase antibody (anti TPO), thyroid stimulating hormone (TSH), free T_4 (fT_4), free T_3 (fT_3) values, and pituitary gland magnetic resonance imaging (MRI) and US reports were evaluated.
Results
It was found that 45(39.5%) patients had thyroid nodule (13 solitary, 32 multiple). ten patients were administered thyroidectomy, and differentiated thyroid cancer (DTC) was detected in six of these patients (5.3%). One patient had lung metastasis. Control group consisted of 113 individuals (101 females, 12 males, mean age 32.1 ± 9.1). In US, 28 of these individuals (24.8%) had thyroid nodule (five solitary, 23 multiple). One individual (0.8%) had DTC.
Conclusion
When compared to control group, thyroid volume and thyroid nodularity were significantly higher in patients with prolactinoma (respectively, $P < 0.001$, $P = 0.018$), however, no statistically significant difference was available for the incidence of thyroid cancer ($P = 0.196$).

DOI: 10.1530/endoabs.37.EP740

EP741

Squamous cell carcinoma of the sphenoid sinus presenting as a sellar mass

Chin Ee Ong, Timothy Peng Lim Quek, Melvin Khee Shing Leow & Daniel Ek Kwang Chew
Tan Tock Seng Hospital, Singapore, Singapore.

Introduction
We present a rare case of squamous cell carcinoma of the sphenoid sinus presenting as a sellar mass and panhypopituitarism.
Case presentation
A 60-year-old Chinese male with schizophrenia and a 20 pack year smoking history, was admitted to our hospital with headache and diplopia without visual field loss. Brain imaging with computed tomography (CT) and magnetic resonance imaging (MRI) revealed a 2.9 cm sellar mass based in the sphenoid sinus, bulging into the suprasellar cistern with post contrast enhancement and pituitary stalk thickening. The optic chiasm was indented, with involvement of the cavernous sinuses and superior portion of the clivus. Subsequent hormonal investigations revealed panhypopituitarism (central hypocortisolism, hypothyroidism and hypogonadism) with hyperprolactinaemia likely from pituitary stalk compression and anti-psychotic medication. There were however no symptoms of central diabetes insipidus (DI). Hormonal replacement with oral hydrocortisone and thyroxine was commenced. An initial biopsy showed focal moderate to severe keratinising dysplasia but no definite invasive malignancy, and a repeat biopsy was planned. Repeat imaging done for worsening symptoms 2 weeks later showed an increase in the size of the sellar mass to 4 cm. Trans-sphenoidal debulking surgery was carried out, and intra-operative biopsy and frozen section revealed the diagnosis of squamous cell carcinoma. Staging CT scans did not reveal any lymph node or distant metastases. Post operatively, patient developed central DI with a biphasic pattern. In view of the advanced intracranial involvement of the tumour, palliative chemotherapy and radiotherapy was planned but patient unfortunately developed progressive worsening neurological deficits likely from tumour progression and passed away.
Conclusion
Squamous cell carcinoma of the sphenoid sinus can rarely present as a sellar mass. Although pituitary adenomas are the most common cause of sellar masses, atypical features such as pituitary stalk thickening or central DI necessitate a high index of suspicion to look for other causes.

DOI: 10.1530/endoabs.37.EP741

EP742

Tumour regrowth in growth hormone deficient adults with non-functioning pituitary adenomas using growth hormone replacement therapy – a sub-analysis from the Dutch National Registry of growth hormone treatment in Adults

Nadège van Varsseveld[1], Christa van Bunderen, Anton Franken[2], Hans Koppeschaar[3], Aart Jan van der Lely[4] & Madeleine Drent[1]
[1]VU University Medical Center, Amsterdam, The Netherlands; [2]Isala Clinics, Zwolle, The Netherlands; [3]Emotional Brain and Alan Turing Institute for multidisciplinary health research, Almere, The Netherlands; [4]Erasmus Medical Center, Rotterdam, The Netherlands.

Objective
Growth hormone treatment (GHT) is a widely accepted treatment in growth hormone deficient (GHD) adults with nonfunctioning pituitary adenoma (NFPAs). However, concerns remain about the safety of GHT, because of its potentially stimulating effect on tumour (re)growth. The aim of this study was to evaluate tumour progression in NFPA patients using GHT.
Patients and methods
From the Dutch National Registry of growth hormone treatment in adults, a nationwide surveillance study in severe GHD adults (1998–2009), all NFPA patients with >30 days of GHT were selected ($n = 783$). Anonymized data of all patients were thoroughly and retrospectively collected from the start of GHT in adulthood (baseline). Recurrent tumour after apparent complete remission at baseline and regrowth of residual tumour were both defined as tumour progression.
Results
Tumour progression developed in 12.5% of the patients after a median time of 2.2 (0.14–14.9) years. Median follow-up time for patients with and without tumour progression was 5.1 (0.2–20.2) and 6.0 (0.71–5.2) years respectively ($P = 0.10$). After adjustment for age and gender, initial radiotherapy decreased the risk of developing tumour progression compared to no initial radiotherapy (Hazard ratio (HR) = 0.16, 95% confidence interval (CI) = 0.09–0.26). Analysis in 577 patients with available baseline imaging data showed that, after adjustment for age and gender, residual tumour at baseline increased the risk of tumour progression compared to no residual tumour (HR = 3.7, 95% CI 2.0–6.8).
Conclusions
In this large cohort of adult NFPA patients using GHT tumour progression was observed in 12.5% of the patients. Pituitary radiotherapy decreased the risk of developing tumour progression, while the presence of residual tumour at baseline increased this risk. More large studies, ideally long-term randomized studies, are needed to provide conclusive evidence with regard to the safety of GHT in GHD patients with a (treated) NFPA.

DOI: 10.1530/endoabs.37.EP742

EP743

Symptoms and comorbidities at diagnosis of 472 acromegalic patients diagnosed between 2009 and 2014

Philippe Caron[1], Thierry Brue[2], Philippe Chanson[3], Gérald Raverot[4], Antoine Tabarin[5], Anne Cailleux[6], Brigitte Delemer[7], Peggy Pierre Renoult[8], Aude Houchard[9] & Frédérique Dupuis-Siméon[9]
[1]Larrey University Hospital, Toulouse, France; [2]La Timone University Hospital, Marseille, France; [3]Bicêtre University Hospital, Kremlin Bicêtre, France; [4]Neuro-Cardiologic Hospital, Bron, France; [5]Haut-Levêque Hospital, Pessac, France; [6]Charles Nicolle University Hospital, Rouen, France; [7]Robert Debré University Hospital, Reims, France; [8]Bretonneau University Hospital, Tours, France; [9]Ipsen Pharma SAS, Boulogne Billancourt, France.

Introduction
Acromegaly is characterised by chronic, excessive secretion of GH and increased IGF1 levels caused by benign pituitary adenoma. This study aimed at describing the symptoms and comorbidities of acromegaly at diagnosis, in a large cohort of patients diagnosed between 2009 and 2014.
Methods
Observational, cross-sectional, multicentre study conducted in France between September 2013 and June 2014. Adult patients with acromegaly diagnosed for <5 years were included. Data were collected retrospectively from patient medical files and confirmed by patients' questionnaires.
Results
472 patients were analysed. Age (mean $\pm$ S.D.) was 51.9 (± 14.3) years and 57.2% were female. BMI was 27.7 (± 5.3) kg/m^2. Time since diagnosis was 30.6 (± 17.8) months. Acromegaly was most frequently diagnosed by endocrinologists

(29.5%) and general practitioners (16.1%). GH- and GH/PRL-secreting pituitary adenomas were reported in 78.8% and 18.2% of patients, respectively. Most patients had a macroadenoma (80.3%). At diagnosis, GH level was 18.7 (±30.1) µg/l and IGF1 level was 295 (±160) %ULN. Among patients with GH/PRL adenoma, serum prolactin level was 183 (±650) µg/l.
At diagnosis, patients presented morphological signs (coarse facial feature, enlargement of hands and feet) (96.2%), skin manifestations (85.8%), respiratory problems (83.5%), asthenia (79.2%), osteoarthropathies (76.1%), endocrine complications (73.3%), tumour mass effects (69.1%), weight gain (64.6%), cardiovascular diseases (62.9%), ear-nose-throat disorders (62.1%), carpal/cubital tunnel syndromes (58.1%), gastrointestinal symptoms (57.8%), sexual dysfunctions (47.7%), metabolic abnormalities (42.8%) ((diabetes mellitus (27.5%), impaired glucose tolerance (9.5%)), psychologic changes (28.8%), and malignant diseases (11.9%). Overall, mean time between symptom or comorbidity onset and diagnosis of acromegaly was 5.1 (±4.3) years.
Conclusion
This study provides insights on symptoms and comorbidities of acromegalic patients recently diagnosed. Results confirm the broad range of comorbidities at diagnosis and the delay for the diagnosis of acromegaly, and therefore emphasise the efforts needed in improving the early recognition of the disease.
Disclosure
Grant from Ipsen Pharma SAS.
DOI: 10.1530/endoabs.37.EP743

EP744

Symptoms of gonadal dysfunction are more predictive of hypopituitarism than non-specific symptoms in screening for pituitary dysfunction following moderate or severe traumatic brain injury

Martin Cuesta Hernandez[1], Mark J Hannon[1], Rachel K Crowley[1], Lucy Ann Behan[1], William Tormey[2], Daniel Rawluk[3], Mark Delargy[4], Amar Agha[1] & Christopher J Thompson[1]
[1]Academic Department of Endocrinology. Beaumont Hospital/RCSI Medical School, Dublin, Ireland; [2]Department of Chemical Pathology, Beaumont Hospital/RCSI Medical School, Dublin, Ireland; [3]National Neurosurgery Unit, Beaumont Hospital/RCSI Medical School, Dublin, Ireland; [4]National Rehabilitation Unit, Beaumont Hospital/RCSI Medical School, Dublin, Ireland.

Context
The economic and logistic burden of screening for hypopituitarism following moderate/severe traumatic brain injury (TBI) is considerable. Published guidelines suggest prioritisation for screening of patients with symptoms of pituitary dysfunction.
Objective
To evaluate the implementation of targeted symptom-based screening for hypopituitarism after moderate/severe TBI, compared with routine consecutive screening.
Design
Group 1 (G1); consecutive patients were screened. Group 2 (G2); screening targeted based on symptoms of pituitary dysfunction. Setting: G1 patients were recruited from the Irish National Neurosurgery Centre and in G2 on symptom based referral from external caregivers. Patients: G1, 137 patients (113 male) and G2 111 patients (77 male) referred for pituitary evaluation (G2).
Main outcome measures
The rate of pituitary hormone deficiency between groups.
Results
Patients with menstrual dysfunction ($n=10$) had more GH (50% vs 11%, $P=0.001$), ACTH (60% vs 14%, $P<0.0001$) or gonadotrophin (90% vs 16%, $P<0.0001$) deficiency and any pituitary hormone deficit (100% vs 33%, $P<0.0001$) than G1. Men with symptomatic hypogonadism ($n=12$) had more GH (33% vs 11%, $P=0.03$), gonadotrophin (58% vs 16%, $P<0.0001$) and TSH (16% vs 1%, $P=0.03$) deficiency than G1. Patients with non-specific symptoms ($n=89$) were no more likely to have hypopituitarism than those consecutively screened. The rates of GH (19% vs 11%, $P=0.12$), ACTH (14% vs 14%, $P=0.99$), TSH (3% vs 1%, $P=0.34$), ADH (7% vs 2%, $P=0.44$) or any pituitary hormone deficit (25% vs 33%, $P=0.21$) were not different between those referred with non-specific symptoms in G2 and G1.
Conclusions
Symptoms of hypogonadism are sufficiently predictive of hypopituitarism to justify inclusion in protocols for screening for hypopituitarism after moderate/severe TBI. Non-specific symptoms of hypopituitarism are no more predictive than systematic screening in identifying pituitary hormone deficits: their place as indicators for screening is therefore questionable.
Disclosure
The work in this study was supported by unrestricted grants from Pfizer Pharmaceuticals and Novo Nordisk Pharmaceuticals.
DOI: 10.1530/endoabs.37.EP744

EP745

A 5 years retrospective studies looking at trends in water deprivation tests and roles for endocrine specialist nurses

Phillip Yeoh[1], Pierre Bouloux[1,2], Shern Chew[1], Bernard Khoo[1,2], Paul Carroll[1,3] & Ashley Grossman[1,4]
[1]Endocrinology & Diabetes Department, The London Clinic, London, UK; [2]Department of Endocrinology, Royal Free Hospital, London, UK; [3]Department of Endocrinology & Diabetes, St Thomas NHS Trust, London, UK; [4]Department of Endocrinology, University of Oxford, Churchill Hospital, Oxford, UK.

Performing water deprivation test (WDT) and prolonged water deprivation test (PWDT) is some of the roles undertaken by endocrine nurse in specialist endocrine units. These tests need to be done in a safe and control environment.
Objectives
To provide safe information to patients to avoid fluids overload when they arrive for the tests. Can the specialist endocrine nurse make clinical decision to terminate the test base on clinical evidence and at what point the communication with consultant is crucial in order to collect results of clinical relevance?
Methodology
35 patients who completed WDT and PWDT over the last 5 years were studied.
Results
Three with overt normal (ON), five with normal (N), three with nephrogenic diabetes insipidus (NDI), 14 with cranial diabetes insipidus (CDI), two with primary polydipsia (PP), eight were excluded due to inability to complete their tests or lack of diagnosis and medical information. ON has the highest mean urine/serum osmolarity ratio at begin and termination of tests. Delay DDAVP during WDT is useful in some cases.
ADH measurement at Peak urine osmolarity can be used to distinguish NDI from CDI. Primary Polydipsia urine/serum osmolarity Ratio increase according to the length of fluid fasting.
Conclusions/recommendations
Address fluids overloading with patients who are coming for these tests. The length of fluids fasting before these tests will be based on patient's symptoms. Endocrine specialist nurse can make clinical decisions if the tests are overtly normal or serum osmolarity goes above 305 mOsm/kg. Additional markers such as ADH and serum sodium can be useful if needed at certain point during the tests.
DOI: 10.1530/endoabs.37.EP745

EP746

The effect of intra-articular glucocorticoid injections on hypothalamic-pituitary-adrenal-axis function: a review

Philip C Johnston[1], M Cecilia Lansang[1], Soumya Chatterjee[2] & Laurence Kennedy[1]
[1]Department of Endocrinology, Diabetes and Metabolism, Cleveland Clinic, Cleveland, OH, USA; [2]Department of Rheumatic and Immunologic Diseases, Cleveland Clinic, Cleveland, OH, USA.

Background
The use of intra-articular (IA) glucocorticoids for reducing pain and inflammation in patients with osteoarthritis, rheumatoid arthritis, and other inflammatory arthropathies is widespread among primary care physicians, specialists and non-specialists in the United States. Injectable glucocorticoids have anti-inflammatory and analgesic properties which can be effective in improving clinical parameters such as pain, range of motion, and quality of life. After injection into the IA space, glucocorticoids may be systemically absorbed; the degree of absorption can depend on the size of joint injection, the preparation used, the dosage and frequency of injection. The adverse effects of IAGC can often be overlooked by both the patient and physician who administer them, in particular the potential deleterious effect on the hypothalamic-pituitary-adrenal (HPA)-axis which can result in adrenal suppression and/or iatrogenic Cushing syndrome.
Aim
We provide an overview on the often under-recognised effects of IAGC on HPA-axis function.

Results and conclusions
IAGC can result in a sharp decline in cortisol to low or undetectable levels within the first days after administration. HPA-axis suppression can typically last for up to 4 weeks after a single injection, although recovery of HPA-axis to baseline can take longer depending on the dose and frequency of injections. Considering the widespread use of IA steroid injections and their clinical effectiveness, physicians who administer them need to be aware of the potential risks of HPA-axis suppression and/or iatrogenic Cushing syndrome. Guidelines for the frequency of dosing in addition to defined time intervals between each injection should be clear. High risk populations have the potential to be screened for adrenal suppression and could include those who receive high doses and multiple injections particularly within the previous 6 months. The potential use of the measurement of salivary cortisol in identifying patients who have subtle changes in HPA-axis function remains to be seen.

DOI: 10.1530/endoabs.37.EP746

EP747

Prolactinomas: do age and gender affect clinic?

Farida Nasybullina[1], Gulnar Vagapova[1] & Bakhtiyar Pashaev[2]
[1]Kazan State Medical Academy, Kazan, Russia; [2]Kazan State Medical University, Kazan, Russia.

Objective
To study the effect of age and gender on manifestation of hyperprolactinaemia.
Methods
Patients were examined using generally accepted methods of diagnosis. 207 patients with prolactinomas were divided into two groups: before and after 50 years. It was a retrospective study with no interventions to generally accepted methods of diagnosis and treatment. The outcomes were measured by frequency of hyperprolactinaemia symptoms according to age and gender.
Results
In patients who are <50 years prolactinomas were observed in 91% of women and 9% of men. The main clinical symptoms in women and men were presented by hyperprolactinaemic hypogonadism. Menstrual irregularities were observed in 70% of women, galactorrhoea – in 54%, infertility – in 53%. Macroadenomas were detected in 13% of women. Clinical signs of hypogonadism in men were presented by decreased libido (100%), erectile dysfunction (80%), infertility (6%) and depression (98%). Macroadenomas were diagnosed in 58% of men. In group over the age of 50 years prolactinomas were diagnosed in 61% of women and 39% of men. Clinical manifestation of the disease, both in women and men, was presented by neurological symptoms: headaches – in 86% of women and in 79% of men; visual disturbances – in 56% of women and 78% of men. Macroadenomas were detected in 68% of women and 89% of men.
Conclusion
People of reproductive age developed typical clinical picture of hyperprolactinaemic hypogonadism, which is well recognised in women, while often ignored in men. The frequency of macroprolactinomas with chiasmatic syndrome increases in both sexes over the age of 50 years, that is partly due to the lack of vivid clinical signs of hyperprolactinaemia in the period of menopause.

DOI: 10.1530/endoabs.37.EP747

EP748

Body weight changes in patients with active Cushing disease after transsphenoidal surgery

Philip C Johnston[1], Amir H Hamrahian[1], Robert J Weil[2] & Laurence Kennedy[1]
[1]Department of Endocrinology and Diabetes, Cleveland Clinic, Cleveland, OH, USA; [2]Department of Neurosurgery, Cleveland Clinic, Cleveland, OH, USA.

Background
Successful pituitary surgery in patients with Cushing disease (CD) can result in long term remission and sustained weight loss. We examined rates of body weight changes in the post-operative period (within 6 months) in patients with active CD who underwent transsphenoidal surgery (TSS) and the relationship of weight loss to remission status.
Methods
Clinical data was obtained from a CD database in addition to an online patient medical record (EPIC). All patients with biochemically confirmed active CD underwent their first TSS by a single neurosurgeon at the Cleveland Clinic (October 2004–August 2013). No patients received glucocorticoids during surgery. Initial remission was defined by nadir cortisol <3 ng/dl, ACTH <5 pg/ml within the immediate post-operative period (72 h). Long term remission was defined as 24 h UFC $<$ULN (upper limit of normal), and/or sequential midnight salivary cortisols $<$ULN, and 1mg DST cortisol <1.8 μg/dl.
Results
88 patients (female: 63, male: 25), with a mean age at presentation of 47 years (range 24–87 years), median follow up 52 months (12–118 months) underwent TSS. No significant differences in baseline demographics including pituitary adenoma size ($P=0.25$) and BMI ($P=0.21$) were observed between the two groups. 64: pituitary microadenoma, 24: macroadenoma, 74 (84%) patients had initial remission after surgery, during follow up six of those with initial remission had recurrence. Those with initial remission had greater mean $\pm$S.D. weight loss at 3 months (kg: -8.1 ± 11.3 (initial remission, $n=59$) v 0.8 ± 8.8 (non-remission, $n=12$), $P=0.007$) and at 6 months (kg: -14.5 ± 12.1 (initial remission, $n=46$) v -6.1 ± 12.1 (non-remission, $n=12$), $P=0.045$). Less weight loss or weight gain at three ($P=0.002$) and six ($P=0.014$) months was associated with increased relapse risk.
Conclusions
After TSS for CD, weight loss within the first 6 months is an additional early clinical indicator associated with initial biochemical remission.

DOI: 10.1530/endoabs.37.EP748

EP749

The development and validation of a new burden and needs assessment questionnaire for patients with pituitary diseases: the BNQ-pituitary

Cornelie Andela[1], Margreet Scharloo[1], Steven Ramondt[2], Jitske Tiemensma[1,2], Ad Kaptein[1], Alberto Pereira[1], Noëlle Kamminga[1] & Nienke Biermasz[1]
[1]Leiden University Medical Center, Leiden, The Netherlands; [2]University of California, Merced, CA, USA.

Background
An increasing number of studies assess quality of life (QoL) in patients with pituitary diseases. At present, available disease-specific QoL questionnaires do not completely cover the patient perspective of QoL. Furthermore, there are no disease-specific questionnaires available which inventories patient's needs for help for impairments in QoL.
Objective
To develop and validate a disease-specific QoL questionnaire for patients with pituitary diseases based on the patient perspective on QoL, which also incorporates the needs for help: the burden and needs assessment questionnaire for patients with pituitary diseases (BNQ-Pituitary).
Methods
337 patients with pituitary diseases fill-out the BNQ-Pituitary and eight other psychosocial questionnaires (i.e. EuroQoL-5D, SF-36, MFI-20, HADS, UCL, GSE, IPQ-brief, IPA). Items were formulated based on results of a recent focus group study of our department. Construct validity was examined by using an exploratory factor analysis with oblique rotation on principal components. Reliabilities were calculated with Cronbach's α, and concurrent validity was measured by calculating Spearman correlations between BNQ-Pituitary reported burden and subscales of the other questionnaires.
Results
The exploratory factor analysis revealed seven subscales (i.e. Mood, Cognitive functioning, Illness perceptions, sexual functioning, social functioning, anxiety, physical complaints) containing a total of 33 items. Subscales reliabilities were all >0.736 and strong and consistent correlations were observed between BNQ-Pituitary scores and scores on the other psychosocial questionnaires. A significant effect of type of pituitary disease was observed, with patients with Cushing's disease reporting the highest burden compared to patients with prolactinoma or non-functioning pituitary adenoma.
Conclusion
The BNQ-Pituitary is a valid and reliable instrument to measure not only the burden of pituitary disease, but also the need for help considering the consequences of the disease. Furthermore, the BNQ-Pituitary can facilitate the efficient assessment of patients' unmet needs. We postulate that paying attention to potential unmet needs may positively affect QoL.

DOI: 10.1530/endoabs.37.EP749

EP750

Rate of Prolactin suppression can predict future prolactin normalisation, tumour shrinkage and time to remission in male macroprolactinomas

Amit Tirosh[1,2], Carlos Benbassat[1,2] & Ilan Shimon[1,2]
[1]Endocrine Institute, Rabin Medical Center, Petah Tiqva, Israel; [2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

Introduction
Dopamine agonists are the mainstay treatment for prolactinomas, but clinical characteristics that predict their effects on prolactin (PRL) suppression and tumour shrinkage are missing. Our study aimed to find measures in early follow-up of men harbouring macroprolactinomas, that will predict dynamics of PRL decrease and adenoma shrinkage.
Methods
A single centre historical prospective study, including a consecutive group of 71 men with pituitary macroadenomas ($\geq$10 mm) and hyperporlactinaemia (>7xULN), treated medically with cabergoline. Comparisons of PRL normalisation rates were performed according to PRL levels achieved at 6 months, maximal adenoma shrinkage during follow-up, and other patient characteristics. Correlations were performed to identify characteristics of PRL suppression dynamics.
Results
Five patients had nadir PRL levels $\geq$x 3 ULN (51 ng/ml), and showed slower response to treatment with cabergoline with consistently higher PRL levels compared to other patients throughout follow-up (6 months mean PRL levels, 519$\pm$403 vs. 59$\pm$118 ng/ml, $P<0.001$). PRL levels after 6 months of treatment correlated positively with current PRL levels ($r=0.74$, $P<0.001$), with adenoma diameter following treatment ($r=0.38$, $P=0.01$), and with time to PRL normalisation ($r=0.75$, $P<0.001$). Shrinkage of adenoma size depicted by first MRI on treatment correlated with maximal adenoma shrinkage during follow-up ($r=0.56$, $P=0.006$).
Conclusions
Six months PRL level might serve as a surrogate marker for PRL normalization and adenoma shrinkage dynamics among men harbouring macroprolactinomas. Among these patients with persistent hyperprolactinaemia at 6 months, higher PRL levels are associated with resistance to cabergoline.

DOI: 10.1530/endoabs.37.EP750

EP751

Endonasal endoscopic pituitary adenoma resection

Václav Masopust[1], David Netuka[1], Vladimír Beneš[1], Ondrej Bradáč[1], Josef Marek[2], Václav Hána[2] & Michal Kršek[2]
[1]Department of Neurosurgery, Central Military Hospital, 1st. Medical Faculty of Charles University, Prague, Czech Republic; [2]Department of Internal Medicine, General Teaching Hospital, 1st Medical Faculty of Charles University, Prague, Czech Republic.

Introduction
In the past 10 years, endoscopic resection of pituitary adenomas has become an alternative to microsurgical resection with the additional advantage of increasing the patient's postoperative comfort. This analysis explored whether endoscopic resection can reduce the risk of postoperative neurohypophyseal dysfunction.
Material and methods
We rated and compared the need to administer desmopressin during the first four postoperative days and with the need after a follow-up of at least 3 months (chronic administration). Two groups of patients were compare: Patients in group 1 were operated on microscopically. Patients in group 2 were operated on endoscopically. Group 1 was made up of 50 patients treated in 1999, group 2 comprised 50 patients operated on from 2006 to 2007.
Results
In group 1 the need to use desmopressin postoperatively occurred in eight patients: three needed chronic treatment. In group 2 the need for postoperative application of desmopressin occurred in four patients, none required chronic treatment.
Conclusions
Endoscopic surgery is a safe and effective method for the resection of pituitary adenomas. The rate of chronic desmopressin application was reduce.
Disclosure
NT13631-4.

DOI: 10.1530/endoabs.37.EP751

EP752

The comparison of echocardiographic parameters, carotid intima thickness, arterial stiffness and plasma soluble CD40 ligand levels in active and inactive acromegalic patients

Guven Baris Cansu[1], Nusret Yilmaz[1], Atakan Yanikoglu[2], Sebahat Ozdem[3], Aytul Yildirim[2], Gultekin Suleymanlar[4] & Hasan Altunbas[1]
[1]Akdeniz Universty Faculty of Medicine, Endocrinology and Metabolism, Antalya, Turkey; [2]Akdeniz Universty Faculty of Medicine, Cardiology, Antalya, Turkey; [3]Akdeniz Universty Faculty of Medicine, Biochemistry, Antalya, Turkey; [4]Akdeniz Universty Faculty of Medicine, Nephrology, Antalya, Turkey.

Introduction
In acromegalic patients, the increased mortality and morbidity are generally due to cardiovascular, metabolic, respiratory and cerebrovascular diseases, so early diagnosis and treatment of cardiovascular lesions may save lives. The aim of this study is to find out the any possible difference in terms of carotid intima media thickness (CIMT), indices of arterial stiffness, soluble CD40 ligand (sCD40L) and some echocardiographic parameters between active and inactive acromegalic patients.
Methods
The study involved 26 active, 24 inactive acromegalic patients and 20 healthy subjects. 47 of 50 acromegalic patients had underwent transsphenoidal surgery and 41 of 50 patients were using somatostatin analogues at least 6 months and nine patients have no treatment after transsphenoidal surgery. CIMT, arterial stiffness, sCD40L and some echocardiographic parameters were compared.
Results
The study showed that CIMT and indices of arterial stiffness were higher in acromegalic group ($P=0.003$ and $P=0.008$ respectively). Left ventricular diastolic dysfunctions were comparable between groups, whereas the left ventricle mass index, DOPPTEI and left atrial diameter were higher, and ejection fraction was lower in acromegalic patients. CIMT, arterial stiffness, sCD40L and parameters of echocardiography were comparable in patients with active and inactive patients.
Discussion
Getting the disease under control hormonally didn't cause a reduction in the subclinical cardiovascular risk. This can point out that in acromegalic patients the structural and functional damage may be due to long-term exposure to excess growth hormone/IGF1.

DOI: 10.1530/endoabs.37.EP752

EP753

An audit of transsphenoidal surgery on nonfunctioning pituitary adenomas

Dolores Moure, Javier Santamaría, Ihintza Larrañaga, Pedro González, Sara Valle & Sonia Gaztambide
Endocrinology and Nutrition, Cruces University Hospital, Barakaldo, Spain.

Introduction and objective
Clinically nonfunctional pituitary adenomas are relatively an uncommon disease. The aim of this work is to describe the clinical characteristics and to review the results of transsphenoidal surgery (TS) of pituitary adenomas in a reference centre.
Methods
A retrospective study (1995–2014) of 66 patients (50% men) diagnosed with pituitary adenomas by a magnetic resonance imaging (MRI) was conducted. demographic, clinical, biochemical data and the results of TS were collected. For statistical processing program SPSS version 22.0 was used.
Results
The mean age of the patients was 57$\pm$16'8 years. The most frequent clinical presentations were as an incidental pituitary mass (34.8%) and visual symptoms (36.4%). The mean size of the sellar tumour was 26.6$\pm$8.8 mm. A 59% of them had pathological visual field testing (34.8% bitemporal hemianopsia). Some hormone deficiency was found in 66.7% of patients before surgery (16.7% of them presented panhypopituitarism). 52 out of 66 were referred for surgery, 49 because of the optic chiasm compression and three due to pituitary apoplexy. The mean size of the tumour was 28.55 mm in those who underwent surgery Vs 20.1 mm in nonsurgical patients ($P<0.001$). Transsphenoidal approach was used in all patients (endoscope visualisation in 13/52). 12 months after the surgery, 50% had no tumour image on MRI. Some hormone deficiency was detected in 90.4% (38.5% of whom had panhypopituitarism) and the visual field deficits improved in 30%. Nine out of 52 patients required a second surgery and 11/52 received radiotherapy due to residual mass.

Conclusion
Considering tumour size results they are similar to those reported in the literature but with a higher risk of hypopituitarism.

DOI: 10.1530/endoabs.37.EP753

EP754

Optic neuropathy following radiotherapy for Cushing's disease followed by the diagnosis of pituitary carcinoma

Krystallenia Alexandraki, Georgios Boutzios, Georgios Nikolopoulos, Panagoula Roussaki, Maria Chrysochoou, Eleftherios Chatzellis, Marina Tsoli, Maria Kaltsatou, Panagiotis Moschouris & Gregory Kaltsas
Endocrine Unit, Department of Pathophysiology, Laiko Hospital, University of Athens Medical School, Athens, Greece.

Introduction
ACTH-secreting pituitary carcinomas are rare neoplasms but there are not factors till now to predict their aggressive evolution nor a standard practice to their management.
Case report
We report a 43-year-old female patient presented in 1990 with Cushing's syndrome due to ACTH-secreting pituitary microadenoma who had been submitted on trans-sphenoidal surgery with cure as defined by post-operative cortisol serum levels <50 nmol/l. In 2000 she represented with clinical, biochemical and imaging recurrence, hence, 10 years after her first remission. She had repeat surgery similarly with cure as defined by post-operative cortisol serum levels <50 nmol/l but again a recurrence within 2 years. Since, no tumour was documented in imaging studies, she received external beam irradiation (in total a dose as high as 54 Gy) in 2005. However, her hypercortisolaemia was still uncontrolled and she was submitted in bilateral adrenalectomy. Ten months after radiotherapy, the patient was presented with declining visual acuity, and radiation-induced optic neuropathy (RON) was diagnosed. Despite treatment with glucocorticoids and hyperbaric oxygen, her vision did not improve. Two years later she was hyperpigmented with increased ACTH plasma levels. The ACTH plasma levels continued to increase reaching very high levels and in 2010 FDG–PET and conventional imaging confirmed the diagnosis of pituitary carcinoma with multiple liver metastasis and local disease. Since today we are trying to control, her disease with several recent chemotherapeutic and biological agents (cisplatin + etoposide and temozolamide + bevacizumab).
Conclusions
This case implies that the appearance of pituitary carcinoma cannot be excluded by the cure post trans-sphenoidal surgery nor can be prevented by a high dose of irradiation even this is so high to cause RON.

DOI: 10.1530/endoabs.37.EP754

EP755

Mortality of patients with non-functioning pituitary macroadenoma is significantly elevated: systematic analysis of 546 cases in a tertiary referral centre in the UK

Georgia Ntali[1], Cristina Capatina[1], Violet Fazal-Sanderson[1], James V Byrne[2], Simon Cudlip[3], John Ah Wass[1], Ashley B Grossman[1] & Niki Karavitaki[1]
[1]Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK; [2]Department of Neuroradiology, John Radcliffe Hospital, Oxford, UK; [3]Department of Neurosurgery, John Radcliffe Hospital, Oxford, UK.

Introduction
Data on the mortality of patients with non-functioning pituitary macroadenoma (NFA) are very limited.
Aim
To assess the mortality of patients with NFA and factors predicting it.
Patients and methods
All patients presenting to our department with NFA between 1963 and 2011 were studied. Status was recorded as either dead or alive, as of 31st December 2011.
Results
546 patients (333 males) were identified (median age at surgery 58.7 years; range 16.1–94.2). Data on mortality were available for all patients covering a median period of 8 years (range 1 month–48.5 years); 83 patients died (median age 77.8 years; range 36.4–98.3) (causes: cardio/cerebrovascular 32.5%, infections 30.1%, malignancies 28.9%, peri-operatively 1.2%, gastrointestinal hemorrhage 1.2%, suicide 1.2%, unknown 3.6%, and old age 1.2%). The SMR for the total group was 3.62 (95% CI: 2.90–4.47; $P<0.001$), for those diagnosed before 1990 4.66 (95% CI: 2.65–7.63; $P<0.001$) and for those after 1990 3.53 (95% CI: 2.77–4.44; $P<0.001$). Clinical follow-up data (until date of death or date the database was frozen) were available for 436 patients (269 males, median age at surgery 58.5 years (range 16.11–94.19), 203/431 with no or intrasellar remnant – 228/431 with extrasellar remnant after surgery, median follow-up 6.9 years (range 1 month–48.5 years), 111/436 with regrowth of NFA, 188/436 received radiotherapy after primary surgery or for regrowth). Cox regression analysis (univariate approach) demonstrated that amongst age at surgery, NFA regrowth, radiotherapy, sex and extent of removal, the first three were significant predictors of mortality; after multivariate analysis using these three parameters, only age remained an independent significant factor (HR 1.099, 95% CI: 1.073–1.126; $P<0.001$).
Conclusions
Despite the improvement in the last three decades, mortality of patients with NFA remains high. Apart from age, factors related with the management/outcome of the tumour including radiotherapy and recurrence are not independent predictors of mortality in this group of patients.

DOI: 10.1530/endoabs.37.EP755

EP756

Sheehan's syndrome: a rare disease with typical symptoms

Anna Dabrowska[1], Jerzy Tarach[1], Agnieszka Zwolak[1,2] & Anna Oszywa-Chabros[1]
[1]Chair and Department of Endocrinology, Medical University of Lublin, Lublin, Poland; [2]Chair of Internal Medicine, Department of Internal Medicine in Nursing, Medical University of Lublin, Lublin, Poland.

Introduction
The enlarged pituitary gland of pregnancy is susceptible to any compromise to its blood supply. Sheehan's syndrome (SS) occurs as a result of *post-partum* pituitary infarction or haemorrhage and usually leads to hypopituitarism. It can be fatal but clinical manifestations may change from one patient to another and symptoms may not occur for many years.
Methods
We analysed retrospectively five cases of women with SS aged 26–56 years, treated at Endocrinology Department between 2003 and 2014, to describe clinical manifestations. In the studied subjects the diagnosis of SS was made based on medical history, clinical symptoms, hormonal tests, and MRI scans.
Results
Mean age of the patients was 41.00 ± 12.33 years (range 26–56 years). All subjects had typical physical signs of SS. The duration between date of the last delivery and time of diagnosis was 9.82 ± 8.85 years (ranged from 1 month to 19 years). The number of pregnancies was from 1 to 4. We observed typical obstetric history of massive hemorrhage at delivery in three women, two of them received a blood transfusion. In two cases there was no overt obstetric complications. All patients lacked *post-partum* milk production and did not menstruate following delivery. According to the hormonal values, five analyzed women had total or partial secondary hypothyroidism, adrenal cortex failure and hypogonadotropic hypogonadism, prolactin, and GH deficiency. They used therapy such as: hydrocortisone (mean 25.00 ± 7.07 mg/day), levothyroxine (mean 75.00 ± 43.30 μg/day), and sex hormone replacement. Diabetes insipidus was found in one patient but it was transient. She was treated with desmopressin (120 μg/day) for 17 months. MRI scans revealed total or partially empty sella in three women and small (beyond the normal range) pituitary gland in two cases.
Conclusion
Although, SS is not a common disease, it should be remembered about concerning women with pituitary insufficiency developing at different times after delivery.

DOI: 10.1530/endoabs.37.EP756

EP757

Cure rates and survival in patients with acromegaly

Simona Galoiu[1,2], Andreea Suvoiala[2], Mariana Purice[2], Andra Caragheorgheopol[2], Raluca Trifanescu[1,2], Mihail Coculescu[1,2] & Catalina Poiana[1,2]
[1]Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; [2]C.I. Parhon National Institute of Endocrinology, Bucharest, Romania.

Introduction
An improvement of survival in patients with acromegaly was claimed in the last years, with multimodal new therapies.

Aims
To assess cure rates of different therapeutic protocols and the impact of these therapies on survival.
Methods
334 patients (224 F/110 M, mean age 48.1 ± 0.7 years) with acromegaly admitted in a single Neuroendocrinology Department between Jan 2001 and Dec 2013 were retrospectively studied by GH, IGF1 levels at baseline and at final visit, therapy, pituitary failure, and date of the death. PAMCOMP computation program calculated standardized mortality ratio (SMR). Kaplan–Meier curve was used to compare the impact of different therapies on survival. Serum GH levels were measured by IRMA (sensitivity 0.1 ng/ml).
Results
35.02% patients obtained control of acromegaly: 17.3% were cured after neurosurgery and/or radiotherapy and additionally 17.6% were controlled by medication. Cure rate for surgery was 17.7% (35/197) and 15.03% (23/153) for radiotherapy. 49/128 (33.5%) patients treated by somatostatin receptor analogues (SSA), 8.3% (4/48) treated with dopamine agonist and 6/16 patients (37.5%) treated by GH receptor agonist were adequately controlled. All causes mortality ratio was similar with general population: SMR = 1.07 (95% CI 0.70–1.52), average follow-up of 2252.11 person-years (median 6.9 years). Females with last GH above 2 ng/ml had a high SMR = 2.51 (95% CI 1.37–4.22).
Operated patients with/without medication and/or radiotherapy had a better survival than untreated patients (rank log Mantel-Cox: $P = 0.04$ operated vs untreated patients, 0.05 operated + SSA patients vs untreated and 0.02 operated + irradiated vs untreated).
Conclusions
Patients with acromegaly and posttreatment GH level ≥ 2 ng/ml had a high mortality, especially women. Surgery treated patients, with additionally treatment for postoperatory remnants, had a better survival, similar with general population.
Disclosure
This work received financial support through the project 'CERO – Career profile: Romanian Researcher', grant number POSDRU/159/1.5/S/135760, cofinanced by the European Social Fund for Sectoral Operational Programme Human Resources De.

DOI: 10.1530/endoabs.37.EP757

EP758

Implementation of clinical guidelines on the cancellation of dopamine agonists in the event of pregnancy in patients with hyperprolactinaemia tumour origin

Julia Gallinger[2], Ekaterina Pigarova[1] & Larisa Dzeranova[1]
[1]Endocrinology Research Centre, Moscow, Russia; [2]Lomonosov Moscow State University, Moscow, Russia.

Aim
Clinical guidelines recommend the cancellation of dopamine agonists after confirmation of pregnancy as because further their use is unnecessary. However, an implementation of these recommendations in real clinical practice is unknown which became the aim of our present research.
Materials and methods
The study included 21 patients with prolactinomas who had 26 pregnancies ended in childbirth. These patients were found archived medical records of Endocrinology Research Centre (Moscow, Russia) and consent to personal/telephone interview to complete specialized survey questionnaire.
Results
In the period up to 6 weeks dopamine agonists have been cancelled in 46% of patients (12/26) of those 42% (5/12) were taking bromocriptine and 58% (7/12) cabergoline. Toxicosis was observed in 8.3% (1/12), intrauterine growth retardation (IUGR) in 16.7% (2/12), and threatened miscarriage in 16.7% (2/12). For more than 6 weeks dopamine agonists took 54% (14/26) of patients, with 29% (4/14) taking bromocriptine, 64% (9/14) – cabergoline and in one patient took quinagolide (7%). In this group toxicosis was observed in 21% (3/14) of cases, IUGR in 7% (1/14), and threatened miscarriage in 21% (3/14). The patient on quinagolide was not aware of the need to discontinue the drug at pregnancy. At 8th week of gestation she had a threatened miscarriage, which doctors regarded as quinagolide-mediated and the drug was canceled; this pregnancy proceeded uncomplicated, ended in term delivery of a healthy child. Another patient with microadenoma as advised by a doctor took cabergoline during whole pregnancy, despite the absence of symptoms of tumor growth and normal otherwise state of health; she had a term delivery, the child had patent foramen ovale. In one case, the dose of cabergoline was gradually decreased till 20 weeks of gestation; first trimester of this pregnancy was complicated by toxicosis; the child was born at term and later was found to have adrenal incidentalomas.
Conclusions
Our study show not ubiquitous implementation of clinical guidelines in the issue of cancellation of dopamine agonists at pregnancy confirmation with 54% patients continuing medications for more than 6 weeks of gestation.

DOI: 10.1530/endoabs.37.EP758

EP759

Alterations in thyroid hormone levels following GH replacement exert complex biological effects

Nigel Glynn[1], Helena Kenny[2], Tarik Salim[1], David J Halsall[3], Gerard Boran[4], Paul Cook[5], Diarmuid Smith[1], Tommy Tun[6], John H McDermott[6], William Tormey[1], Chris J Thompson[1], Brendan McAdam[1], Donal O'Gorman[2] & Amar Agha[1]
[1]Beaumont Hospital and RCSI Medical School, Dublin, Ireland; [2]Dublin City University, Dublin, Ireland; [3]Addenbrooke's Hospital, Cambridge, UK; [4]Adelaide and Meath Hospital, Dublin, Ireland; [5]University Hospital Southampton, Southampton, UK; [6]Connolly Memorial Hospital, Dublin, Ireland.

Introduction
Alterations in the hypothalamic–pituitary–thyroid axis have been reported following GH replacement, with a decline in circulating T_4 concentration the most consistent finding. However, the clinical significance of GH-induced alterations in circulating levels of thyroid hormone is unclear.
Aim
To examine the relationship between changes in serum concentration of thyroid hormones and known biological markers of thyroid hormone action.
Methods
We performed a prospective study of 20 hypopituitary adult men before and after routine GH replacement. Serum TSH and thyroid hormone (free T_4, total T_4, free T_3, total T_3, and reverse T_3) were measured before and after GH substitution. Changes in thyroid hormone concentrations were compared to alterations in serum biomarkers of thyroid hormone action. Resting energy expenditure (REE) and cardiac systolic time intervals were also evaluated as sensitive markers of thyroid hormone exposure.
Results
The mean daily dose of GH was 0.34 ± 0.11 mg. Following GH replacement, free T_4 levels declined as expected (−1.28 ± 0.44 pmol/l, $P = 0.02$). Reverse T_3 levels also fell (−3.44 ± 1.42; $P = 0.03$) and free T_3 levels increased significantly (+0.34 ± 0.15; $P = 0.03$). REE did not rise as expected with GH substitution. SHBG and CK levels were unchanged. However, ferritin, copper, and caeruloplasmin declined suggesting reduced hepatic exposure to thyroid hormone (−26.8 ± 8.5; $P = 0.005$); (−1.7 ± 0.63; $P = 0.02$); and (−0.02 ± 0.01; $P = 0.04$). Complex alterations in lipid profile, including a rise in large HDL particles (+1.75 ± 0.69; $P = 0.02$) and Lp (a) (+12.5 ± 4.7; $P = 0.002$) as well as a fall in intermediate density lipoprotein concentration were variably associated with changes in thyroid hormone and GH. Cardiac systolic time intervals were unchanged. Observed changes in thyroid hormone biomarkers were more pronounced in subjects with multiple pituitary hormone deficiencies.
Conclusion
Our study demonstrates that GH replacement does not improve the biological actions of thyroid hormone in adults.
Disclosure
This work was supported by an unrestricted educational grant from Merck Serono.

DOI: 10.1530/endoabs.37.EP759

EP760

Assessment of mean platelet volume in acromegaly and its relation with disease outcome

Berrin Cetinarslan, Ozlem Zeynep Akyay, Alev Selek, Adnan Batman, Zeynep Canturk & İlhan Tarkun
Endocrinology and Metabolism, Kocaeli University, Kocaeli, Turkey.

Background
Acromegaly is associated with increased risk of coronary atherosclerosis and cardiovascular mortality. Changes in coagulation and fibrinolysis markers in acromegalic patients have been shown to indicate increase in the risk of developing cardiovascular disease. Mean platelet volume (MPV) is a marker of platelet functions and activity, and increased MPV is an independent risk factor of myocardial infarction and thrombotic events. In this study, we examined the levels of MPV in acromegalic patients before and after treatment compared to a control group.

Methods
A total of 80 patients (24 were diabetic) treated in our clinic with the diagnosis of acromegaly between 2009 and 2014 and 65 (23 were diabetic) age- and gender-matched healthy controls were reviewed retrospectively. Demographic data of all subjects and postoperative cure and remission with medical management among acromegalic patients were recorded. Preoperative and postoperative MPV values as well as MPV values observed in patients with controlled disease on medical treatment were compared. In both groups HbA1c levels and their relationship with MPV were also evaluated.
Findings
In this study, 47% of the acromegaly patients and 48% of the control subjects were females. The mean age both groups and the mean HbA1c among diabetics in both groups were similar. MPV values were significantly higher in both the diabetic and non-diabetic acromegaly patients compared with the control subjects. Postoperative MPV values were significantly reduced compared to preoperative values in patients cured with surgery. Patients who achieved control with medical therapy after the failure of surgical intervention demonstrated MPV values similar to those reported in patients cured with surgery. When MPV values at presentation were evaluated in the acromegaly and control groups, it was shown that presence of diabetes mellitus, age and gender had no effect on MPV.
Conclusion
MPV can be considered as a marker for atherothrombotic process and prognosis of acromegalic patients.

DOI: 10.1530/endoabs.37.EP760

EP761

A rare case of papillary thyroid cancer: pituitary metastasis

Ozlem Zeynep Akyay, Berrin Cetinarslan, Ilhan Tarkun, Zeynep Canturk, Alev Selek & Adnan Batman
Endocrinology and Metabolism, Kocaeli University, Kocaeli, Turkey.

Introduction
Differentiated thyroid carcinoma (DTC) rarely represents with distant organ metastasis. Cerebral metastasis is seen in 0.4–1.2% of patients with distant organ metastasis. There are only 14 patients of DTC with pituitary metastasis reported in the literature. Here, we report a papillary thyroid carcinoma (PTC) patient represented with pituitary metastasis.
Case
A 68-year-old male patient has admitted to our hospital with a growing tumour on his anterior chest wall. On imaging there was a 5 cm mass on the manubrium sterni. The patient was referred to our clinic as the biopsy of the mass revealed PTC metastasis. During clinical evaluation there was 5 cm hypoecoic, hypervascular nodule on left thyroid lobe. Also, there were high fluorodeoxyglucose (FDG) affinity on pituitary region, thyroid left lobe, sternum, first lumber vertebrae and left humerus on positron emission tomography–computerized tomography (PET–CT) consistent with metastasis. Total thyroidectomy with lymph node dissection was performed and pathology revealed poorly differentiated insular type PTC. The pituitary lesion was also operated but could only be partially resected. The pituitary pathology showed PTC metastasis. The sternal mass could not be operated due to high morbidity and invasiveness. Radiofrequency ablation was performed but the mass was continued grow. After 3 months arterial embolisation was performed to the lesion. As the pituitary lesion was very close to the brain stem structures, radio-iodine treatment was decided to be contraindicated. 36 Gy conventional radiation therapy was given to the pituitary region. During all these treatment procedures sorafenib 2×400 mg/day medical treatment was also initiated. He is still as follow up with stable disease.
Result
The pituitary metastasis of PTC is a rare entity. The management strategy of distant organ metastasis of PTC should include multidisciplinary approach.

DOI: 10.1530/endoabs.37.EP761

EP762

Adult inpatients on desmopressin: a patient safety initiative using e-prescribing

Adam Bonfield[1], Winston Crasto[2], Elizabeth Hackett[3] & Helena Gleeson[4]
[1]Department of Emergency Medicine, University Hospitals Leicester, Leicester, Leicestershire, UK; [2]Department of Diabetes and Endocrinology, University Hospitals of Leicester, Leicester, Leicestershire, UK; [3]Pharmacy Department, University Hospitals of Leicester, Leicester, Leicestershire, UK; [4]Department of Endocrinology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, West Midlands, UK.

Background
Errors made with critical medicines such as desmopressin and hydrocortisone used in the treatment of endocrine conditions in hospitalised patients can undermine patient safety but are largely preventable.
Methods
Retrospective audit of adult patients admitted at the University Hospitals of Leicester NHS Trust between January 2013 and June 2014, prescribed desmopressin for cranial diabetes insipidus (CDI) or other medical conditions using electronic prescribing (ePMA). Safety concerns were recorded on a scoring system according to pre-defined parameters including patient confusion, abnormalities of serum sodium levels, evidence of missed or delayed administration of desmopressin and hydrocortisone.
Results
15 patients (seven males) with a median (IQR) age of 56 (17–85) years were identified. 31 hospital admissions were recorded with a median length of stay of 5 days (range 1–30). Among eight patients (17 hospital admissions) with CDI, history of confusion was observed in 12 admissions (70%), six admissions (35%) had abnormal admitting serum sodium levels, and 14 admissions (88%) had 39 missed/delayed doses of desmopressin. Common reasons included, medications unavailable (64.9%), no reason mentioned (15.8%), patient declined (7.0%) and nil orally or wrong timing of medication (12.3%). At least one dose of hydrocortisone was missed in 35.7% admissions. In the non-CDI cohort, seven patients had 14 admissions and in 64% admissions there were 18 missed/delayed doses of desmopressin. At least one safety concern was seen at every hospital admission in the CDI patient group.
Conclusion
Errors in critical medications such as desmopressin in prescribing and administration can affect patient safety and cause clinical harm. Increased pharmacovigilance and robust policies supporting medicines management of desmopressin in clinical areas are of paramount importance and will continue to be needed.

DOI: 10.1530/endoabs.37.EP762

EP763

When the improbable happens: a case of acromegaly diagnosed during pregnancy

Carolina Faria, Sílvia Guerra & Mário Mascarenhas
CHLN–Hospital de Santa Maria, Lisboa, Portugal.

Introduction
Pregnancy in a patient with acromegaly is uncommon, as the enlarging pituitary adenoma suppresses gonadotropin secretion rendering the patient amenorrhoeic and infertile. About 40% of the women with pituitary adenomas also have hyperprolactinaemia, which further decreases the likelihood of pregnancy.
Case report
A 32-year-old woman was sent to our centre in the first trimester of pregnancy with the diagnostic of gestational diabetes. Clinical examination revealed acromegalic features. Her blood pressure was normal. A few weeks before getting pregnant, because of a history of headaches and amenorrhoea, she underwent a brain magnetic resonance imaging (MRI) that showed a pituitary macroadenoma, with left cavernous sinus invasion but without compression of the optic chiasma. However, this result became available when she was already pregnant. Hormonal profile revealed elevated GH (80 ng/ml) and IGF1 (1442 ng/ml). Prolactin was also mildly elevated (38 ng/ml). She had no changes in visual acuity, visual fields, or fundus. She was medicated only with insulin for her diabetes, with excellent control. Serial visual field monitoring was performed, which remained normal, and signs and symptoms of acromegaly were stable. She delivered a full-term baby girl by caesarean section, healthy and without any malformations. Three months later, octreotide 20 mg once a month was started, with progressive decrease in GH and IGF1. After 6 months of treatment, a new MRI was performed showing a significant reduction of the tumour. She is now under octreotide 30 mg once a month and about 1 year after the beginning of somastostatin analogue the IGF1 level is 578 ng/ml, GH 3 ng/ml, and prolactin 19.7 ng/ml. Her acromegalic features had regressed.
Conclusion
Pregnancy in women with acromegaly can have a normal course, without obstetrical or foetal complications, and treatment can be postponed to the *postpartum* period.

DOI: 10.1530/endoabs.37.EP763

EP764

Pituitary adenoma in the elderly: a 10 years experience

Sandra Pekic Djurdjevic[1,2], Mirjana Doknic[1,2], Dragana Miljic[1,2], Marko Stojanovic[1], Milan Petakov[1,2] & Vera Popovic[1,2]
[1]Neuroendocrine Unit, Clinic for Endocrinology, Diabetes and Diseases of Metabolism, University Clinical Center, Belgrade, Serbia; [2]Medical Faculty, University of Belgrade, Belgrade, Serbia.

Background
Pituitary adenoma (PA) is an under-investigated pathology in the elderly.
Objective
To review our case records of patients >70 years with PA, in order to evaluate presentation symptoms, hormonal results, and pituitary morphology.
Patients
48 patients aged 70 years or older (21 females/27 males) were identified from the group of 610 patients with PA (7.9%) diagnosed at Neuroendocrine Unit, Clinic for Endocrinology, Belgrade, between 2005 and 2014. Median age in our group of elderly was 73 years (range 70–83).
Results
Thirty-six patients had nonfunctioning pituitary adenoma (NFPA), seven patients had acromegaly (ACRO), four patients had prolactinoma (PRL), and one patient had ACTH secreting PA. In majority of patients ($n=44$; 92%) macroadenoma was diagnosed (20–46 mm in diameter). Pituitary microadenoma was diagnosed in four patients (three ACRO and one NFPA). The commonest presenting symptoms were visual deterioration ($n=23$; 48%) and headache ($n=22$). Hyponatremia (due to secondary hypocorticism) was diagnosed in eight patients (17%). In five patients (all with hyponatremia and hypocorticism) loss of consciousness was the leading symptom. Other patients (20%) reported dizziness ($n=5$), loss of memory, confusion, and depression ($n=5$). In four patients (8%), the disease was incidentally discovered during CT or MRI for cerebral ischemic attacks. Endocrinological evaluation showed global anterior hypopituitarism in 18 patients (38%) and partial hypopituitarism in seven patients (15%; four patients had GH and gonadotropin deficiency and three patients had GH, gonadotropin, and TSH deficiency). Twenty-eight patients (58%; 24 NFPA, three ACRO, and one silent PRL) underwent transsphenoidal surgery, with no severe perioperative complications. Immunohistochemistry was performed in 12 patients (seven NFPA were positive for gonadotropins, one NFPA was GH sparsely granulated, and four NFPA patients were null cell PA). Ki-67 antigen expression was indicative of low proliferative activity.
Conclusion
In the last 10 years pituitary adenomas have been recognised more frequently in the elderly. Most were non-functioning pituitary macroadenomas which presented with visual deterioration and hypopituitarism. If hyponatremia is diagnosed in the elderly with PA, then it can be a life-threatening condition.

DOI: 10.1530/endoabs.37.EP764

EP765

Effectiveness and tolerability of lanreotide in acromegaly: a German database analysis

Christina Dimopoulou[1], Sylvere Störmann[2], Jochen Schopohl[2], Johanna Faust[1] & Günter Karl Stalla[1]
[1]Department of Endocrinology, Max Planck Institute of Psychiatry, Munich, Germany; [2]Medizinische Klinik und Poliklinik IV, Ludwig-Maximilians University, Munich, Germany.

Introduction
Somatostatin analogues (SSA) present the treatment of choice in patients with previously poorly controlled acromegaly.
Methods
We conducted a retrospective analysis of acromegalic patients enrolled in the Network of Excellence for Neuroendocrine Tumors Munich and treated with the SSA lanreotide.
Results
Fifty-six acromegalic patients (25 females; mean age 59 years; 33 with macroadenoma) switched to lanreotide from previous medical therapies for acromegaly ($n=33$; 19 due to insufficient biochemical control, 14 due to poor treatment tolerability) ($n=11$ switch from dopamine agonists, $n=15$ switch from octreotide, $n=3$ switch from pegvisomant, and $n=4$ switch from combination therapy) or were medically treatment-naïve ($n=23$). Of the 56 patients, 29 patients started on 60 mg, four patients started on 90 mg, and 20 patients started on 120 mg lanreotide; three patients started on combination therapy with dopamine agonists or pegvisomant. Mean follow-up time on lanreotide were 4.6 ± 4.6 years. Lanreotide led to clinical improvement of acromegalic signs and symptoms in 96%. Mean GH concentration decreased from 10.5 ± 25.9 to 3.2 ± 4.9 ng/ml after 3–6 months ($P=0.017$) and to 2.6 ± 3.2 ng/ml ($P<0.001$) at the last evaluation on lanreotide (GH ≤2.5 ng/ml in 44 and GH ≤1.0 ng/ml in 37 patients). Mean IGF1 concentration decreased from 1.6 ± 1.0 to 1.1 ± 0.5 xULN after 3–6 months ($P<0.001$) and to 0.8 ± 0.3 xULN ($P<0.001$) at the last evaluation on lanreotide. Acromegaly was biochemically controlled in 20 and 73% of patients at baseline and at the last evaluation on lanreotide respectively. Additionally, lanreotide had significant favorable impact on patients' glycemic status, leading to significant decrease of fasting plasma glucose after 3-6 months of treatment (157.4 ± 141 mg/dl vs 106.9 ± 20.9 mg/dl; $P<0.001$). Lanreotide was well tolerated with the exception of transient mild gastrointestinal discomfort in 21%.
Conclusion
The SSA lanreotide alone or in combination is safe, effective and well-tolerable in the treatment of previously poorly controlled acromegaly.
Disclosure
This work was supported by an independent research grant from IPSEN.

DOI: 10.1530/endoabs.37.EP765

EP766

The metabolic relevance of angiopoietin-like protein 4 in different states of GH/IGF1 excess or deficiency

Nicoleta Cristina Olarescu[1,2], Anders P Jørgensen[1], Ansgar Heck[1], Kjersti R Normann[1,2], Kristin Godang[1] & Jens Bollerslev[1,2]
[1]Section of Specialized Endocrinology, Department of Endocrinology, Oslo University Hospital, Rikshospitalet, Oslo, Norway; [2]Faculty of Medicine, University of Oslo, Oslo, Norway.

Context
Angiopoietin-like protein 4 (Angptl4) is a protein involved in lipolysis, that is regulated by non-esterified free fatty acids (FFA). GH promotes lipolysis and increases circulating FFA. Hypothesis: GH increases circulating Angptl4 levels by modulating its expression and secretion from fat and muscle. Angptl4 might be of metabolic relevance for the insulin resistance associated with GH/IGF1 excess or deficiency.
Objective
To evaluate Angptl4 in acromegaly (ACRO) and adult onset GHD (aoGHD) before and after treatment. Furthermore, to assess the *in vitro* effects of GH/IGF1 on Angptl4 gene expression and protein secretion in human visceral (VA) and subcutaneous (SC) adipocytes, hepatocytes, endothelial cells (HUVEC), and rat H9C2 muscle cells.
Design and patients
Body composition (DXA), glucose metabolism parameters, FFA and Angptl4 were measured in two study populations: a cohort of patients with ACRO at baseline ($n=94$) and after treatment ($n=58$), and a cohort of patients with aoGHD ($n=39$) before, and after receiving GH substitution (9 months, placebo/controlled).
Results
At baseline Angptl4 was positively associated with serum FFA (ACRO, $r=0.48$, $P<0.001$ and aoGHD, $r=0.47$, $P=0.003$). Angptl4 was correlated with body fat ($r=0.46$, $P=0.027$) in aoGHD, whereas no correlation with body fat or glucose metabolism parameters was found in ACRO. In ACRO Angptl4 decreased (62 (40) ng/ml vs 54 (30) ng/ml, $P<0.001$) and FFA did not change (0.509 ± 0.22 mEq/l vs 0.516 ± 0.23 mEq/l, $P=0.633$) with treatment. The decrease of Angptl4 was associated with the decrease of GH ($r=0.55$, $P=0.005$). In aoGHD Angptl4 (54 (28) ng/ml vs 74 (37) ng/ml, $P<0.001$) and FFA (0.471 ± 0.19 mEq/l vs 0.557 ± 0.22 mEq/l, $P=0.009$) increased significantly during active treatment. The increase of Angptl4 was strongly associated with the increase of FFA ($r=0.70$, $P<0.001$). *In vitro* GH, but not IGF1, increased *Angptl4* gene expression and protein secretion from mature SC and VA adipocytes, effect blocked after the addition of GH receptor antibody. No effect was recorded in human hepatocytes, HUVEC and rat muscle cells.
Conclusion
i) GH increases Angptl4 in patients, an effect most probably mediated by the circulating FFA. ii) Angptl4 does not directly regulate glucose homeostasis associated with GH/IGF1 excess or deficiency. iii) Adipocytes, respond to GH stimulation, and should be considered a source of Angptl4.

DOI: 10.1530/endoabs.37.EP766

EP767

Response to pasireotide in an acromegalic patient with resistance to conventional medical treatment

María Sonia Gaztambide Saenz, Pedro González Fernández, Ihintza Larrañaga Unanue & María Dolores Moure Rodríguez
Hospital Universitario Cruces, Bizkaia, Spain.

Introduction
Surgery is the primary therapy in most acromelagic patients. When persistent disease is observed, adjuvant medical therapy is used. Pasireotide is a somatostatin analogue (SSA) not approved for acromegaly therapy yet, but with a potentially better response, given that it binds to four out of five somatostatin receptors.
Materials and methods
We present the case of an acromegalic patient with resistance to many therapies and response to treatment with pasireotide.
Clinical case
A woman diagnosed in 1993, at the age of 24 years, of GH-producing pituitary macroadenoma (3×2×2.5 cm). She underwent surgery twice, with only partial resection, followed by radiotherapy and medical treatment. She was on s.c. octreotide, with partial response. Later on, bromocriptine was added with no improvement in GH/IGF1 levels. MRI showed empty sella at 1996. In 2001 medical therapy was switched to a dose of 30 mg of octreotide LAR/4 weeks plus a maximum tolerated dose of cabergoline (2 mg/week), without normalisation of IGF1 levels. In 2008 pegvisomant (15 mg s.c. daily) was used, achieving normal levels of IGF1, but causing headache and lipohypertrophy. On 3 days/week administration (120 mg/week), elevation in IGF1 level and persisting lipohypertrophy were observed. We requested compassionate-use treatment with pasireotide 40 mg/4 weeks. First dose on June 6th 2012 and increased to 60 on 2013.

	01/06/2012	01/09/2012	29/08/2014
GH (ng/ml)	33.9	8.0	2.3
IGF1 (101–267 ng/ml)	661	709	261

In November 2013 a basal glucose value of 145 mg/dl and HbA1c 6.7% were observed. Metformin and later on vildagliptin were indicated and glucose control was achieved.
Conclusion
Pasireotide has got a clinical improvement and IGF1 control in this patient. Diabetes is under control on dual therapy.

DOI: 10.1530/endoabs.37.EP767

EP768

Exogenous administration of GH increases linear growth velocity at higher doses during pre- and early puberty in GH deficient short stature children

Urooj Anwar[1], Amjad Rashid Kiani[1], Sadia Saqib[1], Maleeha Akram[1], Gulbin Shahid[2], Osama Ishtiaq[3], Afzaal Ahmad[1], Mazhar Qayyum[1] & Shakeel Raza Rizvi[1]
[1]Department of Zoology, Pir Mehr Ali Shah Arid Agriculture University Rawalpindi, Rawalpindi, Pakistan; [2]The Children's Hospital Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan; [3]Shifa International Hospital, Islamabad, Pakistan.

In GH deficiency (GHD), which is a medical condition caused by problems in the pituitary gland, the body does not produce sufficient amount of GH, resulting in short stature in children. The treatment of GHD short children with exogenous GH increases linear growth velocity (LGV). The present study determined the effect of exogenous GH treatment on LGV, the dose(s) of exogenous GH that effectively impacts LGV and the stage(s) of puberty at which the effect of exogenous GH treatment on LGV is more pronounced. Blood samples, height, weight, and LGV of forty (20 boys and 20 girls) GHD short children were obtained, plasma was separated and plasma concentrations of GH and IGF1 were determined using specific assay systems. Data were analysed using Student's *t*-test and ANOVA. The GHD short children, diagnosed on the basis of low plasma GH, IGF1 and lower responses to stimulation tests, were given varying doses of GH (0.02–1.7 mg/day for 12–42 months) administered intramuscularly at different ages (5–18 years) and stages (pre-, early, mid, and late) of pubertal development. GH replacement therapy caused greater increases in LGV at higher doses at pre- and early puberty in both female and male patients as compared to GH treatment at mid and late puberty. The plasma concentrations of GH and IGF1 increased significantly in all patients as compared to those found prior to GH treatment, which indicates that increases in LGV is secondary to augmentation in IGF1 secretion. In conclusion, the present study demonstrates that patients of GHD grow at a greater rate at higher doses of GH. The current investigation also shows that GH therapy caused higher increases in LGV at pre- and early puberty in both girls and boys through its effects on IGF1.

DOI: 10.1530/endoabs.37.EP768

EP769

Evolution of metabolic and psychiatric disorders after remission of Cushing's disease

Eva Lau[1,4], Joana Oliveira[1,4], Sandra Belo[1,4], Paula Freitas[1,4], AnaIsabel Oliveira[1,4], Eduardo Vinha[1], Lígia Castro[3], Josué Pereira[2] & Davide Carvaho[1,4]
[1]Endocrinology, Diabetes and Metabolism Department, Centro Hospitalar São João, EPE, Porto, Portugal; [2]Neurosurgery Department, Centro Hospitalar São João, EPE, Porto, Portugal; [3]Pathological Anatomy Department, Centro Hospitalar São João, EPE, Porto, Portugal; [4]Faculty of Medicine of University of Porto, Porto, Portugal.

Introduction
Cushing's disease (CD) is a rare endocrine disorder characterized by endogenous hypercortisolism, which is associated with metabolic and psychiatric disorders. It is essential to understand the impact of normalization of serum cortisol in the evolution of these comorbidities.
Aims
To evaluate the evolution of metabolic and psychiatric disorders after biochemical control of hypercortisolism in patients with CD.
Methods
Retrospective observational study of patients with CD who underwent pituitary surgery between January 1998 and October 2013. Clinical data were evaluated at diagnosis and at the last evaluation of hospital consultation. Remission was defined as normal urinary free cortisol and normal plasma cortisol after overnight or low-dose dexamethasone suppression test.
Results
Forty-five patients were included: 87% ($n=39$) females, mean age 38.2 (12.9) years and mean follow-up period 90.4 (56.7) months. After pituitary surgery, remission of CD was observed in 73.3% ($n=33$). Recurrence of CD was detected in 30.3% ($n=10$) of those patients after a mean of 64.4 (36.0) months after the first intervention. At diagnosis, 65.8% were hypertensive, 31.7% diabetic, 41.5% had dyslipidemia, and 46.3% psychiatric disorders. Of the 41 patients in remission at the last evaluation: 29.1% were under the same number of antihypertensive drugs, 20.8% discontinued them, 20.8% reduced their number, 16.7% remained without medication, and 12.5% increased; remission of diabetes occurred in 15.3% of patients and 80% of those who initially were on insulin suspended it; the anti-dyslipidaemic therapy was discontinued in 11.8% and psychotropic drugs were suspended in 55.5%. The mean initial BMI was 32 kg/m^2 and no significant differences regarding BMI were found after biochemical control of hypercortisolism. However, 46% of patients had a reduction in BMI class.
Conclusion
Biochemical control of hypercortisolism seems to improve the associated metabolic and psychiatric disorders in CD. However, as it is not possible to predict the evolution of these comorbidities it is mandatory an appropriate follow-up, evaluation and treatment of these patients.

DOI: 10.1530/endoabs.37.EP769

EP770

Sex-related differences in clinical presentation and outcomes of Cushing's disease: a study from a referral centre

Eva Lau[1,4], Joana Oliveira[1,4], Sandra Belo[1,4], Paula Freitas[1,4], Ana Isabel Oliveira[1,4], Eduardo Vinha[1], Lígia Castro[2], Josué Pereira[3] & Davide Carvalho[1,4]
[1]Endocrinology, Diabetes and Metabolism Department, Centro Hospitalar São João, EPE, Porto, Portugal; [2]Pathological Anatomy Department, Centro Hospitalar São João, EPE, Porto, Portugal; [3]Neurosurgery Department, Centro Hospitalar São João, EPE, Porto, Portugal; [4]Faculty of Medicine, University of Porto, Porto, Portugal.

Introduction
Cushing's disease (CD) presents a marked female preponderance, with a female-to-male ratio of 3–8:1, but whether this skewed gender distribution has any relevance to the presentation and outcomes of CD is not well understood.
Aim
To evaluate sex-related differences in the presentation of CD, as regards: biochemical indices of hypercortisolism; complications of disease and outcomes.
Methods
Observational, retrospective study of patients with CD confirmed on pituitary surgery between January 1998 and October 2013.
Results
We included 45 patients, of whom 39 (87%) were women. The mean age at diagnosis was 38.2 (12.9) years and the mean follow-up period was 90.4 (56.7) months. Diabetes was more prevalent in males (50% vs 26.3%), as well as hypertension (83% vs 61%) and dyslipidaemia (66.7% vs 40.5%). The psychiatric disorders were more frequent in females (56.8% vs 16.7%). Most women (56.8%) presented a microadenoma on MRI; 33% of men had a microadenoma and 50% a macroadenoma. CD remission was found in 74.4% of women who underwent pituitary surgery; in men remission occurred in 66.7%. At diagnosis, there were no significant differences in serum cortisol levels, urinary free cortisol, midnight cortisol or cortisol levels after overnight dexamethasone suppression test. Male patients had higher basal levels of ACTH (106.5 (46.0) pg/ml vs 70.5 (38.7) pg/ml, $P=0.048$) and serum cortisol after 2-day dexamethasone suppression test (40.5 (51.7) μg/dl vs 13.3 (11.0) μg/dl, $P=0.015$). No differences were found in serum cortisol or urinary free cortisol suppression after high-dose suppression test, by sex.
Conclusion
Biochemical indices of hypercortisolism, metabolic and psychiatric disorders, as long as outcomes of CD differed by sex. Understanding this dimorphic pattern may be relevant in order to define the adequate diagnostic work-up and follow-up of these patients.

DOI: 10.1530/endoabs.37.EP770

EP771

Association of hormonal changes with disease severity and mortality rate in critically ill patients

Neslihan Cuhaci[1], Berna Ogmen[2], Cihan Doger[3], Burcak Polat[2], Seval Izdes[4], Reyhan Ersoy[1] & Bekir Cakir[1]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey; [2]Department of Endocrinology and Metabolism, Ataturk Education and Research Hospital, Ankara, Turkey; [3]Department of Intensive Care Unit, Ataturk Education and Research Hospital, Ankara, Turkey; [4]Department of Intensive Care Unit, Faculty of Medicine, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey.

Introduction
Endocrinological and metabolic changes can occur in critically ill patients, which may affect the prognosis and outcome. The hypothalamic–anterior–pituitary axis (HPA) plays a crucial role in the endocrine regulation of metabolic and immunological homeostasis. In this prospective study, we evaluated the pituitary–adrenal–gonadal–thyroid axis in the adult Intensive Care Unit (ICU) patients,their outcome, the association between these hormonal changes and 'The Acute Physiology and Chronic Health Evaluation II score (APACHE II)', Sequential Organ Failure Assessment (SOFA), length of hospitalisation and mortality.
Methods
Patients hospitalised in adult ICU (not for trauma or operation) between January 2014 and January 2015 were enrolled in this study. Severity of illness was assessed by APACHE II and SOFA on admission to the ICU and 15 days later. Blood samples were collected within the first 4 h of ICU admission and 15 days later for measurement of anterior pituitary and end organ hormones.
Results
Total patient number was 157. Eighty-five patients were in survival (S), 72 patients were in the non-survival (NS) group. In the NS group, patients' mean age, APACHE II and SOFA scores at the admission were significantly higher. In the NS group median GH, E_2, and cortisol levels were significantly higher whereas median FSH, LH, fT_3, and fT_4 were lower. Fifteen days after admission, there was significant increase in median IGF1 and ACTH levels and decrease in median cortisol and SOFA scores compared to baseline values. Strongest predictors for mortality were found to be hospitalization length, SOFA score, deltaTSH, and age. None of the other endocrine parameters had an effect on mortality.
Conclusion
In critical illness, activation of the HPA and the cortisol response are essential for survival. Combinations of endocrine parameters may provide better indices than measurement of a single hormone or an APACHE II-based score.

DOI: 10.1530/endoabs.37.EP771

EP772

Indirect immunofluorescence for detection of pituitary antibodies

Nuno Vicente[1], Monica Taylor[2], Luísa Barros[1], Leonor Gomes[1], Dírcea Rodrigues[1], Sandra Paiva[1], Isabel Paiva[1], Daniela Guelho[1], Luís Cardoso[1], Diana Martins[1], Diana Oliveira[1], Patrizio Caturegli[2] & Francisco Carrilho[1]
[1]Serviço de Endocrinologia, Diabetes e Metabolismo, Centro Hospitalar Universitário Coimbra, EPE, Coimbra, Portugal; [2]Department of Pathology, School of Medicine, The John Hopkins University, Baltimore, Maryland, USA.

Introduction
Definitive diagnosis of lymphocytic hypophisitis (LH) lacks a pathological analysis. The detection of pituitary antibodies (PAB) with the current methods presents variable results and its clinical utility is therefore limited. Recently, new methods were released for the interpretation of indirect immunofluorescence (IIF), which can increase the specificity for detection of PAB.
Methods
We evaluated four patients followed in endocrinology consultation with clinical suspicion of LH (patient 1: 49 years old female with pan-hypopituitarism beginning 40 days after delivery and an empty sella on MRI; patient 2: 20 years old male with isolated ACTH deficiency and gynecomastia; patient 3: 59 years old female with previous complaints of severe headache and dyplopia starting at 42 years, MRI showing pituitary enlargement with diffuse enhancement after contrast and pan-hypopituitarism ever since; patient 4: 39 years old male with hypogonadotrophic hypogonadism and autoimmune thyroiditis) and one patient with definitive diagnosis of LH; and patient 5: 27 years old female, with severe headaches beginning 1 week before delivery, MRI compatible with a pituitary macroadenoma with diffuse enhancement after contrast. Detection of PAB by IIF was carried out in a specialised centre. The presence of PAB was considered positive whenever a granular of diffuse cytosolic pattern were present, after using purified IgG and Fc blockade, if necessary.
Results
We obtained positive results in 40% of samples (two out of five). Patient 1: negative; patient 2: mild perinuclear positivity (1+); patient 3: negative; patient 4: cytosolic positivity, granular pattern; and patient 5: cytosolic positivity, diffuse pattern.
Discussion and conclusions
The patient with histological diagnosis of LH exhibits a diffuse cytosolic pattern, as usually happens in pituitary disease of autoimmune etiology. The granular cytosolic pattern of patient 4, which is strongly suggestive of autoimmunity, might establish diagnosis of LH. Detection of PAB by IFI, according to the immunostaining patterns, can help in the classification and management of these patients.

DOI: 10.1530/endoabs.37.EP772

EP773

Clinical characterisation of acromegaloidism in a controlled prospective study

Pablo F Catalina[1,3], Wilfredo Guanipa[1,3], Concepción Páramo[2], Enrique Suárez González[3], Lucas González Matías[3], Elías Álvarez[2] & Federico Mallo[3]
[1]Department of Endocrinology, Pontevedra University Hospital, Pontevedra, Spain; [2]Department of Endocrinology, Vigo University Hospital, Vigo, Spain; [3]Centre for Biomedical Research (CINBIO), University of Vigo, Vigo, Spain.

Acromegaloidisms are usually reported as isolated cases that are not well characterised clinically. Indeed, most such cases were reported several decades ago, part of the reason why our knowledge about this entity is scarce. By contrast, clinical situations suggestive of acromegaly are not so infrequent, in which basal GH and IGF1 levels lie within a normal range, the GH responses to OGTT

challenge are conserved and there is no radiological (MRI) evidence of hypothalamic-pituitary masses. These unclassified patients are considered as individuals with acromegaloidism. We made a systematic study of a cohort of 15 such individuals, comparing them to cases of acromegaly and to healthy controls in a prospective follow-up protocol. The subjects in each group were matched by gender, age and BMI, and they were all submitted to current diagnostic tests for acromegaly, including conventional blood and biochemical tests, oral glucose overload and MRI exploration. In addition, the subjects were evaluated using a previously validated clinical activity scale (ACA index), and they were submitted to ultrasonography (USG) exploration of the carpal tunnel, non-dominant knee cartilage and the thyroid gland. The subjects with acromegaloidism obtained similar ACA scores to acromegaly patients and USG explorations revealed similar alterations to those in acromegaly subjects. Although spontaneously remitting acromegaly is thought to be an unlikely cause of acromegaloidism, periodic follow-up of these subjects is recommended and we provide here a systematic protocol to characterise such acromegaloidism.

Disclosure
This work was supported by funds from Xunta de Galicia (ref. IN845B-2010/148).
DOI: 10.1530/endoabs.37.EP773

EP774

Can use of the European diagnostic pathway improve diagnosis and management of hyponatraemia in a District General Hospital? An audit cycle

Alex Asher, Mazin Sirelkhatim, Stephen Wong & Aye Nyunt
Glan Clwyd Hospital, Rhyl, UK.

Introduction
Despite the commonality of hyponatraemia in everyday clinical medicine it is often a poorly management condition in acute medical patients. A European guideline for diagnosis and management was published in 2014 to address such problems.
Aims
To assess the standard of management of patients with hyponatraemia admitted to the medical departments in a rural District General Hospital. To improve investigation, diagnosis, and management of these patients where necessary.
Methods
A review of medical notes and biochemical tests was carried out for 69 patients admitted to the medical assessment unit with serum sodium below 130 mmol/l over a 3-month period. Adoption of the European guideline diagnostic pathway, creation of an investigation set' and educating junior doctors and nurses were used as tools to improve management. Emphasis was placed on use of urine osmolality and sodium as a first line investigation in the diagnostic process. Subsequent re-review of management after change was carried out for 79 patients over a similar timeframe.
Results
Before change: only 13% of euvolaemic patients had a urine osmolality and sodium performed, only 25% of patients had causative medications stopped and only 45% of all patients had a cause established. After change: 51% of euvolaemic patients had a urine osmolality and sodium performed, 66% of causative medications stopped, and 73% of all patients had a cause established. In patients who had a urine osmolality and sodium performed a 90% diagnostic pick-up rate was found, compared to just 63% in those who didn't.
Conclusions
Investigation and management is often neglected in acute medical patients. Using guidelines, education and support tools for doctors and nurses improvements can be made in both investigation and management of these patients. Our findings support European guidance on use of urine osmolality and sodium early in the diagnostic process.

DOI: 10.1530/endoabs.37.EP774

EP775

Congenital pituitary stalk interruption syndrome with isolated GH and TSH deficiency and Rathke's cleft cyst: an incidental association

Ana Wessling, Raquel Paixão, José Maria Aragüés & Mário Mascarenhas
Endocrinology Department, Santa Maria University Hospital, Lisbon, Portugal.

Introduction
Congenital pituitary stalk interruption syndrome (PSIS) is a rare condition, characterized by the triad (not always complete): absence/hypoplasia of the pituitary stalk, hypoplasia/aplasia of the anterior pituitary and absence or ectopy of the posterior pituitary high signal intensity, on magnetic resonance imaging (MRI). PSIS implies a permanent GH deficiency, in 77% associated with other pituitary hormones deficiencies. The aetiology remains uncertain, but some genes have been implied. Rathke's cleft cysts (RCC) present typically as intrasellar and/or suprasellar benign lesions, the most common incidentally discovered sellar lesions (few mm to 2 cm diameter), with a female:male ratio of 1:3.
Clinical case
A 18-year-old boy was referred from the Pediatric Endocrinology Department, with GH deficiency and central hypothyroidism (CH) diagnosed at the age of 9. Recombinant GH therapy had already been suspended (after 9 years; target height 170 cm achieved) and he was only on levothyroxine. MRI at 8 years of age had revealed a small pituitary gland, absence of the high signal intensity in the posterior pituitary, pituitary stalk atrophy, and a small pineal cyst. Reevaluation showed no other pituitary hormone deficiencies. There were no symptoms of diabetes insipidus. Follow up MRI (23 years old) showed a 7 mm sellar and suprasellar cystic lesion, suggestive of RCC, causing pituitary compression, pituitary stalk hypoplasia, and absence of posterior pituitary bright spot in T1. Until now, 1 year later, his clinical condition remains stable.
Conclusions
In this clinical case, a patient with PSIS had a RCC incidentally diagnosed in a follow up MRI. Paediatric cases have been reported but rarely, as RCCs grow slowly, becoming clinically evident later in life. Symptoms are uncommon and associated with mass effects. As there is compression of the pituitary gland, closed follow-up must be kept. Genetic tests results are pending.

DOI: 10.1530/endoabs.37.EP775

EP776

High diversity of Cushing's disease in patients with corticotrophic macroadenoma

Maria Kurowska, Joanna Malicka & Jerzy S Tarach
Department of Endocrinology, Medical University, Lublin, Poland.

Introduction
In 7–20% of cases, Cushing's disease is due to ACTH-producing macroadenoma. Aim of the study was to present our observations concerning etiologic, clinical, and therapeutic diversity of Cushing's disease in patients with macrocortico-tropinomas.
Material and methods
Retrospective analysis of medical records of nine patients (5F; 4M) hospitalized in 2002–2015.
Results
Four of the patients (2F; 2M) were diagnosed before they were 40 years old (mean age 28.5) and five (3F; 2M), >40 (mean age 50). In 3F tumour was initially discovered as microadenoma. A woman (23) first underwent bilateral adrenalectomy because of inability to neurosurgery and 5 years later Nelson's syndrome developed. In two consecutive females (49 and 52) at the moment of diagnosis MRI revealed microadenomas 9×7 and 5×4 mm respectively. In the first female 2 years after initial neurosurgery consecutive four transsphenoidal reoperations, stereotactic radiotherapy, and bilateral adrenalectomy were conducted. Then she developed Nelson's syndrome. Propter a consecutive rapid tumour's invasion, themozolomide and bevacuzimab were introduced. She died 7 years after the diagnosis. In the second patient tumour regrowth was observed 6 years after the first neurosurgery and because of failure of second adrenalectomy and mild hypercortisolism she was qualified to pasireotyd therapy. In six patients (2F; 4M) the pituitary tumours were initially diagnosed as macroadenomas. One patient with 5 cm tumour and overt hypercortisolism died after craniotomy. Another patient presented cyclic Cushing's syndrome with pituitary macroadenoma discovered after 7 years' observation. In the next patient unique cause of Cushing's disease was Crooke's macroadenoma, refractory to two neurosurgeries with good response to themozolomide. In two cases (1F; 1M) macrocorticotropinomas were discovered as incidentalomas and operated as clinically inactive (silent) tumours. In these patients the tumour recurred 5 years after the first neurosurgery and visible hypercortisolism developed.
Conclusion
Macrocorticotropinomas are very heterogenic group of pituitary tumours with high aetiologic, clinical and therapeutic diversity.

DOI: 10.1530/endoabs.37.EP776

EP777

Changes of prolactinomas during pregnancy and lactation

Larisa Dzeranova[1], Julia Gallinger[2], Ekaterina Pigarova[1], Svetlana Vorotnikova[1], Natalia Bykanova[1], Liudmila Rozhinskaya[1] & OGGO Consortium[3]
[1]Endocrinology Research Centre, Moscow, Russia; [2]Lomonosov Moscow State University, Moscow, Russia; [3]Head Endocrinologists, Federal Districts, Russia.

Aim
To assess the size changers of prolactinomas after pregnancy and lactation.
Material and methods
We have analyzed the Russian register of tumors of the hypothalamic–pituitary region and conducted additional surveys of patients with prolactinomas who had pregnancy. We obtained data from 33 patients with prolactinomas who had 45 pregnancies and MRI studies prior and during/after pregnancy and lactation. Five patients had macroadenomas and 40 microadenomas.
Results
In 55.6% (25/45) of prolactinomas did not change after the pregnancy (including in three patients with macroadenomas). In 20% (9/45) they increased in size, including two macroadenomas. Growth of pituitary adenomas in two cases was accompanied by clinical symptomatology (visual field loss and complete loss of vision in one eye). 22.2% (10/45) of patients experience the decreased in size of prolactinomas, which was observed only with microadenomas, and in three cases complete involution was noted. Information on lactation period and MRI evaluation was available for 34 pregnancies in patients with prolactinomas. According to the recommendations of doctors lactation was stopped immediately after birth with the help of dopamine agonists in 23.5% (8/34) of cases. In 87.5% (7/8) of these patients MRI did not show any changes from baseline and in one patient (12.5%) microadenoma had increased in size to macroadenoma without clinical significance. 26/34 patients nursed their children on average of 12 ($\pm$8) months and often stopped lactation due to doctor's recommendations with the help of dopamine agonists. In these patients according to MRI no changes were found in the pituitary adenoma size in 50.0% (13/26) cases, adenoma decreased in 26.9% (7/26), and increased in 23.1% (6/26). The patients with the increased size of prolactinoma during lactation had the shortest duration of lactation – 5 ($\pm$2) months.
Conclusion
While the majority of pregnancies and lactation in patients with prolactinomas is not associated with adverse complications from the adenoma site, there is still a substantial risk in one in five women to experience tumor growth, though mostly subclinical, which raises the need of better prediction of such unfavorable outcomes.

DOI: 10.1530/endoabs.37.EP777

EP778

Pituicytoma: a rare tumour

Diana Oliveira[1], Leonor Gomes[1], Dírcea Rodrigues[1], Francisco Belo[2], Olinda Rebelo[3], Sandra Paiva[1], Carolina Moreno[1], Daniela Guelho[1], Ana Margarida Balsa[4], Nuno Vicente[1], Luís Cardoso[1], Diana Martins[1] & Francisco Carrilho[1]
[1]Endocrinology, Diabetes and Metabolism Department, Coimbra Hospital and University Centre, Coimbra, Portugal; [2]Neurosurgery Department, Coimbra Hospital and University Centre, Coimbra, Portugal; [3]Neuropathology Laboratory, Neurology Department, Coimbra Hospital and University Centre, Coimbra, Portugal; [4]Endocrinology, Diabetes and Nutrition Department, Baixo Vouga Hospital Centre, Aveiro, Portugal.

Introduction
Pituicytoma is a low-grade glioma of the suprasellar and sellar regions that is rarely described (about 60 cases in the literature). The clinical, laboratory, and neuroradiological findings are not pathognomonic, and therefore definitive diagnosis is only possible after surgery and histopathological study. Total resection is the treatment of choice, since subtotal removal can often lead to recurrence or progression.
Case report
We report the case of a Caucasian male with no significant medical history who develops isolated frontal headache at the age of 48. Magnetic resonance imaging (MRI) revealed an expansive sellar and suprasellar lesion, with 14 mm, well-defined limits, bright homogeneous enhancement with gadolinium, associated with a slight deviation of the optic chiasm. Hormonal study was normal. The patient continued to be followed in Neurosurgery consultation and after 4 years presented complaints of gradually worsening visual disturbances, progressively decreased libido and erectile dysfunction. On visual field testing, a bitemporal hemianopia was noted. MRI revealed millimetrical increase of the tumour. He underwent transnasal/transsphenoidal surgery, which resulted in a partial removal due to difficulty in controlling bleeding. The histopathological examination showed a tumor composed of bipolar cells, with immunohistochemical positivity for vimentin and S100 protein, Ki-67 $<2\%$ – pituicytoma. The postoperative hormone study revealed panhypopituitarism. The control MRI detected significant residual tumour, so it was decided to propose the patient for radiosurgery treatment.
Conclusions
This pituicytoma case illustrates a diagnosis that, although rare, should not be excluded from the possibilities available before a suprasellar or sellar lesion that presents with certain cardinal radiological features. The persistence of significant residual tumour was due to the bleeding tendency of the lesion during surgery. Awareness of the possibitlity of pituicytoma before surgery would be ideal for appropriate treatment planning, with possible preoperative embolisation of the tumour.

DOI: 10.1530/endoabs.37.EP778

EP779

The impact of surgical management of Cushing's disease in pregnancy on foetal outcomes

Philip C Johnston[1], Mahmoud Abbassy[2], Amir Hamrahian[1], Laurence Kennedy[1] & Pablo Recinos[2]
[1]Department of Endocrinology, Diabetes, and Metabolism, Cleveland Clinic, Cleveland Ohio, USA; [2]Neurological Institute, Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center, Cleveland Clinic, Cleveland, Ohio, USA.

Background
Cushing's disease is a condition rarely encountered during pregnancy. It is known that hypercortisolism is associated with increased maternal and foetal morbidity and mortality.
Aims and methods
A comprehensive search of the literature was performed for cases of Cushing's disease in pregnancy including our own case. Analysis was performed of all pregnant patients with Cushing's disease who were treated with surgery compared to a surrogate control group of pregnant patients with untreated Cushing's syndrome. Foetal outcomes were compared including preterm labour, intrauterine growth retardation, intrauterine foetal death, and neonatal death. Cases of Cushing's disease who were not in remission or with missing post-operative data were mentioned but excluded from our statistical analysis.
Results
There were 11 previously reported cases of Cushing's disease surgically managed between the 10th and 23rd weeks of pregnancy. Of those, three cases were excluded due to lack of post-operative biochemical results or follow-up information and one case was excluded due to lack of biochemical remission. Foetal complications occurred as follows: preterm labour 29% (2/7), intrauterine growth retardation 29% (2/7), neonatal death 14% (1/7), and intrauterine foetal death 0% (0/7). Of these, there was a significant reduction ($P=0.04$) in preterm labour when compared to the preterm labour rates occurring in untreated Cushing's syndrome. Other foetal complications were not statistically different. Out of the 11 case reports, maternal and surgical complications included pre-eclampsia ($n=4$), syndrome of inappropriate antidiuretic hormone ($n=2$), diabetes insipidus ($n=1$), cerebrospinal fluid leak ($n=1$). Three patients did not have any maternal or surgical complications.
Conclusions
Transsphenoidal surgery for Cushing's disease can be performed safely during the second trimester of pregnancy. The rate of preterm labour is significantly lowered when Cushing's disease is surgically treated and biochemical remission is achieved during pregnancy.

DOI: 10.1530/endoabs.37.EP779

EP780

Neutrophil/lymphocytes ratio in patients who have hypogonadotropic hypogodanism

Havva Keskin[1], Yasemin Kaya[4], Kenan Cadirci[2], Hakan Gozcu[2], Elif Ziypak[2], Senay Arikan[3] & Ayse Carlioglu[2]
[1]Medeniyet University, Istanbul, Turkey; [2]Erzurum Training and Research Hospital, Erzurum, Turkey; [3]Kirikkale University, Kirikkale, Turkey; [4]Ordu University, Ordu, Turkey.

Introduction
The effects of sex steroids on lymphocytes count and functions are well known and it is propounded that autoimmune diseases more common in women. NLO index is an indicator of inflammative situation. In this study, it has been aimed that neutrophil/lymphocytes ratio (NLO) calculation by determining neutrophil/lymphocytes values in patients who diagnosed as hypogonadotropic hypogodanism and searching that whether there is significant difference between healthy group or not.
Method
33 patients who have been diagnosed as hypogonadotropic hypogodanism, 56 people who have no statistically significant difference in point of age, BMI among them and they are completely healthy people as a control group, totally 89 people have been incorporated to the study. It has been calculated that patient group's age average is 22.4 ± 7.4 and control group's age average is 23.1 ± 6.4. Statistically significant difference couldn't be determined among them ($P=0.6$). Patients' neutrophile and lymphocytes values have been evaluated by studying. Patients' C-reactive protein(CRP) and testosterone levels have been registered again by studying.
Results
In the study results; patient group NLO has been founded as 1.8 ± 1.3 and healthy group NLO has been founded as 1.4 ± 0.3 and statistically significant difference has been determined among them ($P=0.03$). Statistically significant difference has been respectively determined between patient group and healthy group in point of white blood cell count (7.9 ± 3.1 and 6.7 ± 1.1, *P*.0.04), neutrophil (4.6 ± 2.7 ve 3.7 ± 0.7, $P=0.03$), lymphocytes (2.4 ± 0.6 and 2.7 ± 0.7, $P=0.04$) and CRP(2.0 ± 1.3 and 0.9 ± 1.0, $P=0.01$).In the group which has hypogonadotropic hypogodanism; while positive correlation is being determined between NLO ($r=0.228$, $P=0.03$), white blood cell ($r=0.564$, $P<0.001$) and neutrophil ($r=0.847$, $P<0.0001$), negative correlation has been determined between testosterone and lymphocytes count ($r=-0395$, $P=0.001$).
Discussion
We can say that sex steroids can be effective on lymphocytes and neutrophil count depending on the results from this study. Whether to return to normal of sex steroids replacement with these functions must be demonstrated by more detailed studies.

DOI: 10.1530/endoabs.37.EP780

EP781

Childhood onset GH deficiency: re-evaluation at the point of transition to adult care

Mariana Grace[1], Stephen O'Riordan[2], Rose Morissey[2], Mary Stapeton[3] & Susan O'Connell[2]
[1]Department of Paediatric and Child Health, University College Cork, Cork, Ireland; [2]Paediartric Endocrinology Unit, Cork University Hospital, Cork, Ireland; [3]Department of Biochemistry, Cork University Hospital, Cork, Ireland.

Childhood onset GH deficiency (CO-GHD) usually presents with aberrant growth. Treatment is recombinant GH (r-GH) to attain target height. The 2005 European Consensus statement on management of CO-CHD at transition indicates that most adolescents will require repeat GH testing at completion of linear growth. Patients with persistent GHD will require continuation of r-GH for wellbeing, optimal body composition and metabolism. However, there is little data supporting predictors of persistent GHD, which include underlying diagnosis (structural pituitary defects or idiopathic, multiple or isolated pituitary hormonal deficiencies) and serum IGFPB3, IGF1 levels on completion of linear growth.
Objectives
To (1.) classify patients according to European Society of Paediatric Endocrinology Classification of Paediatric Endocrine Diagnoses (Cohort 1) (2.) evaluate patients aged >14 years in this cohort (Cohort 2).
Methodology
A retrospective review of all patients receiving GH treatment ($n=65$) attending a regional tertiary Paediatric Endocrinology centre over an 18 month period, and prospective re-testing of those fulfilling the criteria.
Results
Cohort 1: 47% had primary and 52% secondary growth failure. Cohort 2: 24 patients aged >14 years (75% males), 29% with primary growth failure. 71%had secondary growth failure, of whom 35% had idiopathic GHD (iGHD) (normal pituitary structure), 64% had structural pituitary abnormalities (congenital/acquired). Four patients fulfilled criteria for retesting, all with normal IGF-1 after one month off GH; two had normal GH levels (iGHD) and two had persistent GHD (1 craniopharyngioma and one suspected genetic aetiology due to family history of CO-GHD).
Conclusion
This is the first study of CO-GHD in an Irish cohort. The results are consistent with international literature. In addition, family history of CO-GHD may be a predictor for persistent GHD. We anticipate that >60% of our cohort will have persistent GHD at the time of transition warranting continuation of GH.

DOI: 10.1530/endoabs.37.EP781

EP782

Some clinical characteristics and cardiovascular risk of our patients with hypopituitarism during long-time follow-up

Milica Medic-Stojanoska[1,3], Andrijana Milankov[1,3], Bojan Vukovic[2,3], Tijana Icin[1,3], Ivana Bajkin[1,3], Jovanka Novakovic-Paro[1,3], Ivanka Percic[2,3] & Branka Kovacev-Zavisic[1,3]
[1]Clinical Center of Vojvodina, Clinic for Endocrinology, Diabetes and Metabolic Diseases, Novi Sad, Serbia; [2]Clinical Center of Vojvodina, Emergency Center, Novi Sad, Serbia; [3]Medical Faculty of Novi Sad, University of Novi Sad, Novi Sad, Serbia.

Several studies have pointed to increased morbidity and mortality in patients with hypopituitarism, particularly from cardiovascular diseases, regardless of the application of the substitution therapy. The aim of this study was to present clinical characteristics and cardiovascular risk of our patients with hypopituitarism during 20 years of follow-up.
Methods
Sixty patients with hypopituitarism without patients with acromegaly and Cushing disease were analysed retrospectively/prospectively. The investigated group consisted of 32 men and 28 women, of the average age of 52.18 ± 17.51.
Results
Mean BMI values were 27.78 ± 6.53 kg/m^2. The average age of the examinees at the time of diagnosis was 40.20 ± 18.69. The most common causes of hypopituitarism were pituitary macroadenomas (53.33%) and craniopharyngeoma (21.66%). Partial hypopituitarism with lesion of two and more functions was present in 64.41%, panhypopituitarism in 28.81%, and 6.78% had an isolated deficiency of one adenopituitary hormone. Patients were treated with substitution therapy L-thyroxine, hydrocortisone, growth hormone, sexual steroids, while diabetes insipidus was treated with desmopressin. 6.66% of subjects treated with dietary nutrition regime had diabetes mellitus type 2. The therapy of hypopituitarism was followed by insignificant reduction in systolic and diastolic blood pressure. Elevated values of total cholesterol over the course of therapy significantly decreased ($P\leq0.009$) as well as values of LDL cholesterol ($P\leq0.005$). The values of HDL cholesterol and triglycerides were not significantly changed during treatment. Cardiovascular incidents were recorded in only 11.66% of the subjects, and a lethal outcome in one patient due to sepsis.
Conclusion
The results indicate that the middle aged people are most prone to the risk developing hypopituitarism, mostly due to a tumor in the sellar region and its treatment. Cardiovascular risk factors are present in untreated hypopituitarism. Despite substitution therapy, the ofteness of cardiovascular incidents is present.

DOI: 10.1530/endoabs.37.EP782

EP783

Long-term recurrence in nonfunctional pituitary adenomas after surgery

Maria Galiana Rodriguez Caballero, Nuria Valdés Gallego, Jessica Ares Blanco, Cecilia Sánchez Ragnarsson, Laura Cacho, Joaquín Pertierra de la Uz, Antonio Rabal Artal, Lorena Suárez Gutierrez, Elias Delgado, Pablo Martinez Camblor, Ceferino Faedo & Edelmiro Menéndez Torre
Hospital Universitario Central de Asturias, Oviedo, Spain.

Object
Nonfunctioning pituitary adenomas can experiment recurrence and/or progression (R/P) several years after surgery in about 15–50% of patients. There is few evidence about risk factors that could predict R/P. The aim of this study is to identify them and describe our experience through a long term of follow-up in pituitary macroadenomas.
Methods
Retrospective cohort analysis of 64 patients who underwent surgery between 1990 and 2013. The main outcome was to evaluate prevalence of R/P during the follow-up, based on imaging criteria and identify some risk factors for R/P.

Results
Over a median follow-up of 10.12 years, there was 46% of R/P after surgery at a median time of 4.6 years, the cumulative risk of being free of R/P was 62% by 5 years and decrease to 45% by 15 years after surgery. Multivariate cox proportional hazard regression analysis identified the following risk factors as associated with increased risk of recurrence: radiotherapy after surgery (hazard ratio 2.90, 95% CI 1.15–7.46, $P=0.023$) and the tumour size at diagnosis (hazard ratio 1.05 CI 1.009–1.10, $P=0.019$).
Conclusions
Patients with NFPA need long-term follow-up because they have a high risk of R/P over time. Radiotherapy after surgery decreases the risk of recurrence or progression specially after five years. The tumour size at diagnosis is an independently risk of R/P.

DOI: 10.1530/endoabs.37.EP783

EP784

Recurrence of GH-secreting pituitary adenomas during puberty in children with germline AIP mutations: a clinical challenge

Silvia Filipponi[1], Vincenzo Esposito[1], Adrian F Daly[2], Albert Beckers[2] & Marie-Lise Jaffrain-Rea[1,3]
[1]Neuromed, IRCCS, Pozzilli, Italy; [2]Endocrinology, CHU of Liège, University of Liège, Liège, Belgium; [3]Dept of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy.

Germline AIP mutations (AIP^{mut}) predispose to young onset somatotroph pituitary adenomas (GHPA) and gigantism. AIP^{mut} GHPA are often aggressive and resistant to pharmacological treatment, which may be especially challenging in the paediatric setting. We report our experience with two young Italian AIP^{mut} male patients with incipient gigantism due to childhood pituitary macroadenomas, who both experienced recurrent GH/IGF1 hypersecretion followed by tumour regrowth during puberty.
Case 1
Patient A developed incipient gigantism due to a familial R304X AIP^{mut}. He was successfully operated on at the age of 9 years. for an intrasellar macroadenoma (12 mm). Two years later, spontaneous puberty occurred and IGF1 increased progressively. Final diagnosis of disease recurrence was made at the age of 14.5 years and pharmacological treatment with cabergoline (CAB) and somatostatin analogues (SSA) was started with a partial response.
Case 2
Patient B complained of visual defects at the age of 11.5 years. in a sporadic setting of accelerated growth. MRI showed a pituitary macroadenoma with suprasellar extension (27 mm), which was successfully operated on. Plasma GH/IGF1/PRL and growth velocity normalized. A germline A277P AIP^{mut} was found. Soon afterwards spontaneous puberty occurred and IGF1 increased progressively. Two years later he was started on CAB due to modest biochemical/clinical worsening and initial tumour regrowth. Thereafter, an increasingly aggressive tumour recurrence developed, requiring multiple treatment modalities with SSA, CAB and/or pegvisomant. He was re-operated at the ages of 14 and 18 years. and then underwent radiotherapy. Medical therapy was progressively withdrawn, with no need for hormone replacement therapy currently.
Comments
Both patients completed puberty, with heights stabilising at 191 and 190 cm, respectively. Early diagnosis of disease recurrence is of special importance in patients with incipient gigantism, but this may be very challenging during puberty in the absence of radiological evidence of tumour regrowth.

DOI: 10.1530/endoabs.37.EP784

EP785

Interpretation of dynamic test results in secondary hypocortisolism post pituitary surgery and hydrocortisone replacement doses

Aikaterini Theodoraki[1], Christopher McAlpine[1], Anne Dawnay[1], Neil Dorward[2], Michael Powell[2], Joan Grieve[2] & Stephanie Baldeweg[1]
[1]University London College Hospital, London, UK; [2]National Hospital for Neurology and Neurosurgery, London, UK.

Background
Following pituitary surgery, dynamic testing with insulin tolerance (ITT) or glucagon stimulation testing (GST) is used to identify patients with secondary hypocortisolism who require glucocorticoids. High glucocorticoid replacement doses are associated with adverse effects, and the optimal replacement dose is unknown.
Aim
We aimed to assess the interpretation of dynamic testing post pituitary surgery in clinical practice and its relation with the hydrocortisone replacement doses used.
Methods
Retrospective review of all dynamic testing results post pituitary surgery between 2004 and 2014 in a tertiary centre, and of the medical notes.
Results
101 patients fulfilled the inclusion criteria, out of which 61 (60.4%) were tested with an ITT and 40 (39.6%) with a GST. 27 patients were prescribed glucocorticoids following ITT testing, and 26 following GST. The decision regarding the hydrocortisone dose was made by the trainee or Consultant who had requested the test from clinic. Patients that were prescribed hydrocortisone 20 mg/day had significantly lower peak cortisol levels on dynamic testing compared to patients prescribed 10 mg/day (252 ± 142 nmol/l vs 356 ± 95 nmol/l, $P<0.05$) or emergency steroids only (484 ± 45 nmol/l, $P<0.005$), but no different peak cortisol levels compared to patients prescribed 15 mg/day (313 ± 149 nmol/l). Similarly, patients prescribed 10 mg/day or 15 mg/day had significantly lower dynamic testing peak cortisol compared to patients prescribed emergency hydrocortisone only ($P<0.005$ and <0.05 respectively). There was a trend to treat patients who had with radiotherapy with higher doses of hydrocortisone. Most patients continued the steroid dose recommended post dynamic testing and did not require dose changes in stable conditions with a follow-up of 4.4 ± 3 years. On the day of dynamic testing, patients that failed an ITT or a GST had baseline cortisol of 205 ± 112 nmol/l.
Conclusion
Patients diagnosed with hypocortisolism on dynamic testing post-pituitary surgery require variable dose or emergency only glucocorticoid replacement. The peak cortisol level on dynamic testing is useful when deciding the glucocorticoid replacement scheme.

DOI: 10.1530/endoabs.37.EP785

EP786

Cushing's Syndrome: An ominous and commonly forgotten cause of hypokalaemia

Cherng Jye Seow[1], Zhiguang Ng[1], Claire Min-Li Teo[1], Grace Lum[1], Minyang Chow[1], Chin Ee Ong[1], Tian Ray Lai[1] & Davin Ryanputra[2]
[1]Tan Tock Seng Hospital, Singapore, Singapore; [2]Yong Loo Lin School of Medicine, Singapore, Singapore.

Introduction
We report a patient with hypokalaemia secondary to Cushing's syndrome (CS) to reinforce this commonly forgotten association.
Case report
A 57 years old lady with newly diagnosed hypertension, hyperlipidaemia and diabetes mellitus presented with persistent hypokalaemia for evaluation. She had tinea corporis but otherwise did not look Cushingoid. Investigations: K 2.6 (RI: 3.50–5 mmol/l), HCO_3 35 (RI: 19–31 mmol/l), Urine K/Cr 8.1. Both renin and aldosterone were suppressed. 24 h urinary free cortisol (UFC) was elevated at 1811 (RI: 59–413 nmol/day); 0800 h cortisol after 1 mg overnight dexamethasone suppression test (DST) was elevated at 1156 nmol/l. The patient denied taking any liquorice or corticosteroids. ACTH dependent CS was made with ACTH level of 12.1 pmol/l. Overnight 8 mg DST suppressed the cortisol to more than 50% (1223 nmol/l→ 351 nmol/l). Brain imaging revealed a lytic lesion epicentered in the body of the sphenoid bone, involving the sella and clivus, suspicious for a chordoma. BIPSS was not performed as interpretation may be difficult given the proximity of the lesion to the pituitary. Spironolactone was started to block the mineralocorticoid (MC) effect of cortisol and she was promptly referred to neurosurgery.
Discussion
Activation of MC receptors by cortisol is normally limited due to its conversion to inactive cortisone at the sites of aldosterone action by the enzyme 11-β-hydroxysteroid dehydrogenase type 2 (11-β-HSD2). In ACTH-dependent CS, cortisol secretion exceeds the metabolic capacity of 11-β-HSD2. ACTH inhibits 11-β-HSD2 and there may also be hypersecretion of nonaldosterone mineralocorticoids such as deoxycorticosterone (DOC) and corticosterone. Excess MC activity leads to sodium retention, hypertension, hypokalaemia, metabolic alkalosis, low plasma aldosterone and renin activity. Besides CS, other differentials to consider include 11-β-HSD2 deficiency, liquorice ingestion, Liddle's syndrome, DOC-secreting tumour and certain forms of congenital adrenal hyperplasia.

Conclusion
CS presents with hypokalaemia. Earlier diagnosis and management may improve outcome.

DOI: 10.1530/endoabs.37.EP786

EP787

The effect of pregnancy and lactation on prolactinoma

Wonjin Kim[1], Cheol Ryong Ku[2], Jae Won Hong[3] & Eun Jig Lee[2]
[1]Department of Internal Medicine, Gangnam CHA Hospital, CHA University, Seoul, Republic of Korea; [2]Department of internal medicine, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Department of internal medicine, Ilsan-Paik Hospital, College of Medicine, Inje University, Koyang, Gyeonggi-do, Republic of Korea.

Prolactinoma predominantly occurred in young women of reproductive age. But there are limited data about the effect of pregnancy and lactation on prolactinoma progression. We evaluated the safety of dopamine agonists including bromocriptine and cabergoline and pregnancy outcome in prolactinoma patients. Patients diagnosed with prolactinoma who experienced pregnancies were included. Sellar MRI and serum prolactin levels were performed before and after pregnancy and lactation. Total 46 patients with 62 pregnancies were included. Among 62 pregnancies, spontaneous pregnancies analysed 61 (98.3%) and only one pregnancy was made by IVF. Live births were in 51 (82.3%), while spontaneous abortions occurred in 11 (17.7%). Twenty-one were treated with cabergoline at the time of conception, whereas 28 with bromocriptine. We divided patients into two groups by their changes of adenoma size after delivery; increased ($n=22$) or decreased ($n=15$). Patients with bigger adenoma size before pregnancy showed significantly increased after childbirth. However, the enlarged adenoma did not cause any clinical problems. Of all, breast-feeding was performed in 38 pregnancies. Mean duration of lactation was 4.9 ± 4.4 months. Among those 38, 16 patients had done MRI follow-up after the lactation. There were decreased adenoma sizes in nine patients, no changes in five patients, while increased only in two patients. In conclusion, breast-feeding is not contra-indicated in patients with prolactinoma, especially those who had smaller adenoma.

DOI: 10.1530/endoabs.37.EP787

EP788

Prevalence of the sleep breathing disorders in untreated and treated patients with acromegaly

Yulia Kovaleva, Alexander Dreval, Irena Ilovayskaya, Margarita Krukovskaya, Nikolay Kulakov & Svetlana Fedorova
Moscow Regional Research and Clinical Institute n.a. M.F.Vladimirskiy, Moscow, Russia.

For the purpose to compare sleep breathing disorders (SBD) in untreated and treated patients with acromegaly, we examined 55 patients with acromegaly (18 men and 37 women): 27 patients with newly diagnosed acromegaly, age 56.0 (47.0; 64.0) y.o., BMI 30.2 (27.8; 34.4) kg/m2, GH levels 12.8 (4.6; 23.0) ng/ml, IGF-1 245 (106; 331) % of upper normal limit (UNL), hypertension duration 6.5 (1.0; 14.8) years; 28 patients with treated acromegaly, age 57.0 (47.3; 64.8) y.o., BMI 30.7 (27.9; 35.0) kg/m2, GH levels 2.1 (1.2; 3.4) ng/ml, IGF-1 14 (7; 21) % UNL, hypertension duration 9.0 (3.0; 10.0) years. Data are expressed in Median (25%;75%). Respiratory monitoring was conducted using device ApneaLink, ResMedInc, Australia. Statistical analysis: SPSSv.22. High index of apnoe-hypopnoe (IAH) was found in 91.9% untreated and in 78.6% treated patients: severe SBD in 51.9% and 46.5% patients (IAH 46.6 (40.8; 57.8) and 47.0 (43.9; 59.0), respectively); moderate SBD – in 25.9% and 21.4% (IAH 21.3 (20.0; 23.0) and 23.2 (18.0; 26.3)), mild – in 14.8% and 10.7% (IAH 10.5 (8.3; 12.1) and 5.0 (5.0; 11.0)). The saturation level (normally 94-98%) was decreased in 54.2% untreated and 42.3% treated patients; the average saturation level was 93.0 (90.0; 94.0)% and 94.0 (91.8; 95.3)%, correspondingly. Desaturation level (normally 90-98%) was below normal in 91.7% untreated and 83.3% treated patients; the average desaturation was 79.5 (70.3; 86.8) % and 84 (72.3; 88.8) %, respectively. Severity of SBD did not correlated with GH/IGF-1 levels. Moderate correlations were found between IAH and age, IAH and duration of hypertension. Thus, sleep breathing disorders (with high prevalence of severe IAH and significant desaturation) could be found in most of the patients with untreated and treated acromegaly, and regression of SBD after acromegaly treatment is not so significant. Specific methods of apnoe treatment should be considered for patients with acromegaly and SBD.

DOI: 10.1530/endoabs.37.EP788

EP789

Acrostart: Spanish retrospective study to determine the timeframe to achieve hormonal normalisation with initial Somatuline Autogel® treatment in acromegaly patients in routine clinical practice

Cristina Álvarez Escolá[1], Eva María Venegas Moreno[2], Juan Antonio García Arnés[3], Concepción Blanco Carrera[4], Mónica Marazuela Azpiroz[5], María Ángeles Gálvez Moreno[6], Edelmiro Menéndez Torre[7], Javier Aller Pardo[8], Isabel Salinas Vert[9], Eugenia Resmini[10], Elena María Torres Vela[11], María Ángeles Gonzalo Redondo[12], Ricardo Vílchez Joya[13], María Paz de Miguel Novoa[14], Irene Halperín Rabinovich[15], Concepción Páramo Fernández[16], Antonio Miguel Picó Alfonso[17], Sara Arroyo[18], Francesc Pérez[18] & Eva Pineda[18]
[1]Hospital Universitario La Paz, Madrid, Spain; [2]Hospital Universitario Virgen del Rocío, Sevilla, Spain; [3]Hospital Regional Universitario Carlos Haya, Málaga, Spain; [4]Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Spain; [5]Hospital Universitario de La Princesa, Madrid, Spain; [6]Hospital Universitario Reina Sofía, Córdoba, Spain; [7]Hospital Universitario Central de Asturias, Oviedo, Spain; [8]Hospital Universitario Puerta de Hierro, Majadahonda, Spain; [9]Hospital Universitari Germans Trias i Pujol, Badalona, Spain; [10]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [11]Hospital Universitario San Cecilio, Granada, Spain; [12]Fundación Jiménez Díaz, Madrid, Spain; [13]Hospital General Virgen de las Nieves, Granada, Spain; [14]Hospital Clínico San Carlos, Madrid, Spain; [15]Hospital Clínic Provincial, Barcelona, Spain; [16]Complejo Hospitalario Xeral-Cies de Vigo, Vigo, Spain; [17]Hospital General Universitari d'Alacant, Alacant, Spain; [18]IPSEN Pharma, L'Hospitalet de Llobregat, Barcelona, Spain.

Introduction
This study aimed to determine the timeframe to achieve hormonal normalization considering dosing patterns of Somatuline Autogel (SOM, lanreotide) used in clinical practice.
Methods
From March 2013 to October 2013 clinical data from 62 patients with active acromegaly treated with SOM for ≧4 months who achieved hormonal control (GH levels <2.5 ng/ml and/or normalised IGF1 on ≧two evaluations) at 17 Spanish hospitals were collected into a database. Primary objective was to determine the timeframe from initiating SOM treatment to hormonal normalisation. Secondary objectives included use of health resources, tumour size control, patient satisfaction and adherence.
Results
Non-compliance excluded five patients. Median age of 57 patients was 64 years (23–90), 21 (36.8%) were male, 35 (61.4%) had macroadenoma, 39 (68.4%) had undergone surgery, 14 (24.6%) had received radiotherapy. Median hormonal values at start of SOM treatment were GH: 2.6 ng/ml (95%CI 2.6–7.4), IGF1: 1.6xULN (95% CI 1.6–2.1). SOM 120 mg was the most frequent initial dose (51% patients), with prolonged interval use (≧6 weeks) in 44% patients. Main starting regimens were 60 mg per 4 weeks ($n=13$), 90 mg per 4 weeks ($n=6$), 120 mg per 4 weeks ($n=13$), 120 mg per 6 weeks ($n=6$), 120 mg per 8 weeks ($n=9$). Median length of SOM treatment was 68 months (7–205). Hormonal control was achieved in 4.9 months (95%CI 7.9–20.1). 13 (22.8%) patients managed injections without assistance of health care nurses: 8 (14.0%) were able to self-inject and 5 (8.8%) had injections administered by close relatives. Median number of specialist physician visits until hormonal control was 3 (95%CI 4–10). During SOM treatment tumour shrinkage up to 46.7% was reported in ten patients with available information. 51 (89.5%) patients were 'satisfied'/'very satisfied' with SOM treatment and 49 (86.0%) patients did not miss any doses.
Conclusion
Real-life treatment with SOM led to a fast hormonal control in acromegaly responder patients, with a high treatment adherence and treatment satisfaction, despite disparity of SOM starting doses and interval dosing.
Disclosure
This study was sponsored by IPSEN PHARMA, S.A.

DOI: 10.1530/endoabs.37.EP789

EP790

Prevalence of the sleep breathing disorders in untreated and treated patients with acromegaly

Irena Ilovayskaya, Alexander Dreval, Yulia Krivosheeva, Alexander Abramenko & Galina Stashuk
Moscow Regional Research & Clinical Institute n.a. M.F.Vladimirskiy, Moscow, Russia.

There are some data concerning high prevalence of infrasellar extension of somatotropinomas. To reveal any differences expansion of pitutary macroadenomas with various hormonal secretion, we have analyzed MRI data of 175 pituitary macroadenomas: 87 non-functioning adenomas (NFAs), 48 prolactinomas, 43 somatotropinomas. The sizes of pituitary tumour (vertical, sagittal, frontal): NFAs 24 (17.5; 34.5)mm, 23 (17.4; 28) mm, 23 (18; 30) mm; prolactinomas 21 (15; 31) mm, 20 (16; 30) mm, 20 (14; 30) mm; somatotropinomas – 18 (14; 25) mm, 18.2 (14; 24) mm, ? 17 (14.5; 23) mm. The tumour volume varied: in NFAs from 618 to 68753 mm^3 (median 6620 (2638; 14492) mm^3), in prolactinomas 565–86871 mm3 (median 5365 (1495; 10316) mm^3), in somatotropinomas 352–124501 mm^3 (median 3052 (1696; 5727) mm^3) ($P<0.001$). Prevalence of suprasellar, infrasellar and laterosellar extensions were: NFAs–94, 62, and 39%; prolactinomas – 75, 64 and 62%; somatotropinomas – 61, 75, and 44%, respectively. Suprasellar tumour growth was predominant in NFAs and prolactinomas but not in somatotropinomas ($P<0.001$). Higher frequency of infrasellar growth of somatotropinomas was noted but the difference was not significant in comparison with other tumours ($P>0.05$). Obvious prevalent incidence of laterosellar growth of prolactinomas was observed compared with both NFAs ($P=0.002$) and somatotropinomas ($P<0.016$). Optic chiasm compression according to MRI data was found in 55% of NFAs, 35% of prolactinomas and 19% of somatotropinomas ($P<0.001$) and it was correlated with suprasellar growth and vertical size >18 mm. Thus, in our cohort of patients non-functioning pituitary adenomas have markedly larger volume with predominant suprasellar growth and high frequency of chiasm compression compared with hormonally active pituitary tumours. Prolactinomas and somatotropinomas did not differ in volume, however, had some differences in growth directions: this is the first data concerning high prevalence of laterosellar extension of prolactinomas, predominant infrasellar growth of somatotropinomas was also observed without significant difference in comparison with other pituitary tumours.

DOI: 10.1530/endoabs.37.EP790

EP791

Lung function tests in 109 acromegalic patients

Sylvère Störmann[1], Bodo Gutt[2], Josefine Roemmler-Zehrer[1], Martin Bidlingmaier[1], Jochen Schopohl[1] & Matthias Angstwurm[1]
[1]Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Munich, Germany; [2]Asklepios Klinik Birkenwerder, Abteilung für Diabetologie, Asklepios Klinik Birkenwerder, Abteilung für Diabetologie, Germany.

Introduction
Acromegaly is a chronic disease that affects morphology and organ functions. These changes lead to clinically relevant comorbidities. Untreated acromegaly reduces life expectancy by 10 years, mostly due to cardiovascular events, malignancies and respiratory disorders. We present the results of a series of 109 acromegalic patients at a single institution.
Methods
Lung function tests were performed under standardized conditions in patients with acromegaly treated in our outpatient clinic. Normative data was used to compare our patients (measured value) with healthy controls (predicted value); percentage of predicted value was used to perform subgroup analysis. Criteria of cure were IGF1 in the age- and sex-adjusted normal range and random GH <1.0 µg/dl.
Results
We investigated 109 acromegalic patients without history of pulmonary disease (53 male, 49%) with a mean age of 54.6 ($\pm$13.5) and mean duration of acromegaly of 12.6 years ($\pm$11.6). 20 patients had active, untreated acromegaly at time of assessment. 29 patients were biochemically normalized. Lung function significantly differed from healthy controls in terms of higher volume regarding intrathoracal gas volume, maximal vital capacity, residual volume, total lung capacity, and forced expiratory volume in 1 second. Patients showed signs of obstruction with significantly lower peak expiratory flow and maximum expiratory flow when 75% of the FVC has been exhaled (FEF75/MEF25). 56.5% of patients had a reduced FEF75/MEF25 and 40.4% increased residual volume. There was no significant difference between active and inactive acromegaly. Female patients had significantly smaller flow rates of peak expiratory flow, FEF25/MEF75 and FEF50/MEF50.
Conclusions
In our cross-sectional analysis of lung function in 109 patients with acromegaly lung function volumes were increased compared to healthy controls. Patients showed signs of small airway obstruction at time of diagnosis, unchanged in remission. Subclinical airway obstruction was significantly more pronounced in female patients.

DOI: 10.1530/endoabs.37.EP791

EP792

Thyroid lesions in patients with acromegaly–case-control study

Kosma Wolinski, Adam Stangierski, Edyta Gurgul, Barbara Brominska & Marek Ruchala
Department of Endocrinology, Metaboilsm and Internal Medicine, Poznan University of Medical Sciences, Poznan, Poland.

Introduction
Acromegaly is a disease caused by excessive secretion of growth hormone and subsequently insulin growth factor 1. It is believed that this oversecretion can cause increased prevalence of nodular goiter and thyroid cancer. However, the amount of studies comparing acromegalic patients with control groups is low. The aim of the study was to assess the prevalence of thyroid lesions in patients with acromegaly in comparison with age and sex-matched control group.
Materials and methods
We have searched the medical documentation of patients with acromegaly treated in single endocrine department in the years 2003–2013. The prevalence of thyroid lesions was compared with the group of patients with hormonally inactive adrenal incidentalomas. Thyroid ultrasonography is routine procedure performing in every patient hospitalised in our department.
Results
patients with acromegaly and 184 patients with incidentalomas were included. mean age was 52.6 and 53.9 years respectively (P=0.44), percent of women – 60.5 vs 65.2% respectively (P=0.35). Any thyroid lesions were present in 77.6% of patients with acromegaly and 63.0% with incidentalomas (P=0.002), multinodular goiter in 66.8% vs 47.8% (P=0.0002), thyroid cancer in 5.4% vs 2.7% (P=0.21) respectively. RRs were 1.2 with 95% confidence interval (CI) 1.1–1.4, 1.3 (1.1–1.6) and 2.0 (95% CI 0.7–5.6) respectively. In case of subjects with at least one thyroid lesion, maximal diameter of the biggest thyroid lesion was significantly higher in patients with acromegaly than in control group – median 13.0 vs 9.0 mm (P=0.0008). Also the mean thyroid volume was significantly higher in acromegalic patients (35.5 vs 17.7 cm^3, P<0.0001).
Conclusions
Structural thyroid abnormalities are significantly more common in patients with acromegaly. Our study, performed on one of the largest described groups of acromegalic patients, confirms that systematic thyroid examination should be important part of follow-up in case of patients with acromegaly.

DOI: 10.1530/endoabs.37.EP792

EP793

Anterior pituitary hormone deficiencies in primary and surgery related empty sella cases and its effect on quality of life

Hafize Titiz, Yusuf Aydin, Elif Onder, Alper Koc & Tuba Soysal
Department of Internal Medicine and Endocrinology and Metabolism, Medical Faculty, Duzce University, Duzce, Turkey.

Introduction
Primary empty sella (PES) is often found incidentally during neuroradiological studies. Although pituitary function is usually normal in patients with PES, it could be associated with serious clinical conditions including different degrees of hypopituitarism. Post-operative empty sella (POES), the most common group, results from pituitary adenoma and their treatments. Our aim is to compare anterior pituitary functions and quality of life (QoL) with Short Form-36 (SF-36) between patients with PES (total and partial) and POES.

Material and methods
Totally 75 patients (34 partial, 20 total PES and 21 SES) were evaluated. Basal anterior pituitary and its target hormones were measured. When we determined low basal cortisol levels and/or low insulin like growth factor-1 levels, underwent insulin tolerance test (ITT) or synacten test. After the patient gave informed consent to participate in the study, we performed SF-36 to evaluate the QoL.
Results
We classified the patients according to the radiological findings as partial empty sella (group 1), total empty sella (group 2) and POES (group 3). 9 (26.5%) patients in group 1 didn't have any hormone deficiency however 15 (75%) patients from group 2 and 10 (47.6%) patients from group 3 and 7 (20.6%) patients from group 1 had panhypopituitarism. The ratio of panhypopituitarism was significantly higher in group 2. According to SF-36 scales, Mean score of physical role functioning was significantly higher in group 3. Score of general health perceptions was significantly lower in group 1.
Conclusion
Endocrinological evaluation should be performed during each visit of patients with PES (partial and total) and POES. All hormonal deficiencies should be treated with appropriate medical substitution to maintain the quality of life. QoL in pituitary deficiency were affected in adults, the results showed to physical role functioning and general health perceptions significant difference between groups.

DOI: 10.1530/endoabs.37.EP793

EP794

Multimodal management of GH-secreting pituitary adenomas – the experience of the endocrinology department Tirgu-Mures, Romania, in the last decade

Imre Zoltan Kun[1], Zsuzsa Tanko[2], Anisie Nasalean[2], Jozsef Balazs[2], Camelia Gliga[2,3], Ionela Pascanu[2,4] & Zsuzsanna Szanto[2,4]
[1]Doctoral School, University of Medicine and Pharmacy, Tirgu-Mures, Romania; [2]Clinical Department of Endocrinology, Clinical Hospital Mures County, Tirgu-Mures, Romania; [3]Department of Histology, University of Medicine and Pharmacy, Tirgu-Mures, Romania; [4]Department of Endocrinology, University of Medicine and Pharmacy, Tirgu-Mures, Romania.

Introduction
The diagnostical and therapeutical management of GH-secreting pituitary adenomas has been modified in many aspects in the last decade, and the guidelines also have been considerably changed.
Objective
To evaluate the management of acromegaly applied in an endocrinological clinical unit from Romania, and the efficiency of different therapeutical schemes.
Materials and methods
23 patients with acromegaly, treated and followed-up were included in this study. The positive diagnosis of GH-secreting pituitary adenoma was based on the elevated age-related IGF-1-level, suppressed GH-value >1 ng/ml during oral glucose tolerance test and conclusive hypothalamo-pituitary MRI. The applied different therapeutical schemes (surgery, drugs, radiotherapy and combination), and the efficacy of these – assessed by periodic control of IGF-1-level, suppressed GH-value and MRI – were evaluated.
Results
78.3% of the patients had GH-secreting adenoma, the other 21.7% mixed, GH/PRL-secreting form. At diagnosis the mean suppressed GH-level was 23.2+/−6.8 ng/ml, mean IGF-1-value 784.5+/−139.4 ng/ml, mean adenoma size 17.7+/−2.8 mm. First line therapy was neurosurgery in 14 cases, medical treatment (somatostatine-analogue+/−dopamine-agonist) in six and conventional radiotherapy in three patients, out of which in five cases (21.7%, four after surgery, one after radiotherapy) a good control was achieved. The uncontrolled cases received a second therapeutical procedure, and from them other four cases (17.4%, two reinterventions, one after drug administration and one after radiotherapy) reached a good control. Finally, at eight patients combined multiple therapeutical management (surgery+drug+/−radiotherapy) was applied, and other three cases (13%) been brought under control. During long-term follow-up six patients become non-compliant, and they did not return to reevaluations.
Conclusion
From all the 23 subjects in 52.1% an optimal therapeutic control was achieved with all the applied treatment schemes. Acromegaly could be controlled by monotherapy, mainly neurosurgery in 21.7%, by double treatment scheme in an other 17.4% and by multiple therapeutical combinations in 13% of the cases.

DOI: 10.1530/endoabs.37.EP794

EP795

Early diagnosis and treatment of pituitary apoplexy in a diabetic pregnant woman

Elif Onder[1], Yusuf Aydın[1], Hafize Titiz[1], Tuba Soysal[1], Esra Ozen[1] & Ramazan Buyukkaya[2]
[1]Duzce University Medical Faculty Department of Internal Medicine and Endocrinology and Metabolism, Duzce, Turkey; [2]Duzce University Medical Faculty Department of Radiology, Duzce, Turkey.

Introduction
Pituitary apoplexy results from haemorrhagic infarction of a pre-existing pituitary adenoma or within physiologically enlarged gland. Pituitary apoplexy during pregnancy is rare but serious event with significant morbidity and mortality if not recognised in time. Pituitary apoplexy is characterised by sudden onset of headache, nausea, vomiting, visual disturbances, eye movements restricted and varying degrees of pituitary insufficiency and accompanied by change of consciousness may be clinically overt or as subclinical. Our case report describes a woman who presented with pituitary apoplexy in the 27 weeks of pregnancy.
Case report
A 30-year-old female patient receiving intensive insulin therapy with diagnosis of gestational Diabetes Mellitus. Patient was presented with severe headache, nausea, and vomiting complaints in the 27 weeks of pregnancy. Patient was hospitalised in with urinary tract infection and hyperglycaemia. Early morning serum cortisol was 3.02 μg/dl (6.2–19.4), fT_4:0.57 (*n*: 0.93–1.70) ng/dl and TSH: 0.84 μIU/ml (*n*: 0.34–4.3), other metabolic parameters were within normal limits. Magnetic resonance imaging (MRI) of the pituitary showed pituitary apoplexy. Patient was started with IV 80 mg twice daily and desmopressin nasal spray twice daily. Patient's electrolytes was monitored twice daily. The second day was added to patients levothyroxine 50 μg. Surgery was not planned due to risk of loss of baby. Clinical improvement continued in the following days and after supplementation of methylprednisolone, levothyroxine and desmopressin. Reduction in bleeding site was detected in the control of pituitary MRI. Delivery after 36 weeks of pregnancy was uneventful and a healthy girl was born.
Conclusion
Pituitary apoplexy is a very rare but serious complication that can likely be precipitated by the physiologic changes associated with pregnancy in patients. Because early diagnosis and treatment can and often does result in complete recovery, it is important to recognise and effectively manage this event when it occurs immediately.

DOI: 10.1530/endoabs.37.EP795

EP796

Changes in mid-regional pro-atrial natriuretic peptide during thirsting separate patients with diabetes insipidus from those with primary polydipsia

Sandrine Urwyler[1], Katharina Timper[1,2], Wiebke Fenske[3], Felix Kühn[4], Nica Frech[1], Birsen Arici[5], Jonas Rutishauser[6], Peter Kopp[7], Bruno Allolio[8], Christoph Stettler[4], Beat Müller[9], Mira Katan[10] & Mirjam Christ-Crain[1]
[1]Clinic of Endocrinology, Diabetes and Metabolism, Department of Clinical Research, University Hospital Basel, Basel, Switzerland; [2]Max-Planck-Institute for Metabolism Research, Cologne, Germany; [3]Integrated Research and Treatment Center for Adiposity Diseases, Leipzig University Medical Center, Leipzig, Germany; [4]Division of Endocrinology, Diabetes and Clinical Nutrition, University Hospital Bern – Inselspital, Bern, Switzerland; [5]Department of Internal Medicine, Spital Rheinfelden, Rheinfelden, Switzerland; [6]University Clinic of Internal Medicine, Kantonsspital Baselland, Bruderholz, Switzerland; [7]Division of Endocrinology, Metabolism and Molecular Medicine and Center for Genetic Medicine, Northwestern University, Chicago, Illinois, USA; [8]Department of Internal Medicine I, Endocrine and Diabetes Unit, University Hospital Würzburg, Würzburg, Germany; [9]Division of Endocrinology, Diabetology and Metabolism, Medical University Clinic, Kantonsspital Aarau, Aarau, Switzerland; [10]Department of Neurology, University Hospital Zurich, Zürich, Switzerland.

Background
The water deprivation test as the accepted gold standard in the differential diagnosis of polyuria polydipsia syndrome can be associated with a decrease in extracellular fluid volume in patients with diabetes insipidus (DI). We herein evaluated mid-regional pro-atrial natriuretic peptide (MR-proANP) as marker of extracellular body volume in patients with diabetes insipidus compared to primary polydipsia (PP), at baseline and after water deprivation.

Methods
Patients >18 years old with a history of polyuria and polydipsia were prospectively included. Participants underwent a standardized combined water deprivation and 3% saline infusion test that was terminated when serum sodium levels exceeded 147 mmol/l. MR-proANP levels were determined at baseline and when serum sodium exceeded 147 mmol/l.
Results
55 patients with polyuria polydipsia syndrome were enrolled: 37 had complete or partial DI and 18 had PP. At baseline median MR-proANP levels in patients with DI were similar as compared to patients with PP (median (IQR) 51.2 pmol/l (31.9; 74.4) vs 42.6 pmol/l (28.4; 63.6); $P=0.23$). Upon the water deprivation test, in patients with DI MR-proANP levels decreased to 46.9 pmol/l (29; 64.1) ($P=0.004$), whereas there was no change in patients with PP (45.8 pmol/l (26.1; 61.3), $P=0.28$). The change of MR-proANP was significantly more pronounced in patients with DI compared to patients with PP ($P=0.009$). A delta-ANP of >0.9 had an AUC of 0.77 (95% CI, 0.63–0.90) with a sensitivity of 75.7% and a specificity of 72.2% to differentiate patients with DI from patients with PP.
Conclusion
MR-proANP levels decrease upon a water deprivation test in patients with DI, without a change in PP. Changes in MR-proANP during thirsting may separate patients with diabetes insipidus from those with PP.
Disclosure
This work was supported by the Swiss National Foundation (grant number PP00P3-123346) and Thermo Scientific Biomarkers, Henningsdorf, Germany, the developer and manufacturer of the MR-proANP-Assay, who provided all the kits for measurement of MR-proANP levels.
DOI: 10.1530/endoabs.37.EP796

EP797

Cardiovascular risk factors and metabolic parameters in GH deficient patients

Zoe A Efstathiadou[1], Sideris P Delaroudis[2], George N Koukoulis[3] & Marina D Kita[1]
[1]Department of Endocrinology, 'Hippokration' General Hospital of Thessaloniki, Thessaloniki, Greece; [2]Department of Endocrinology, 424 General Military Hospital, Thessaloniki, Greece; [3]Endocrine Unit, Department of Internal Medicine, University of Thessaly School of Medicine, Larissa, Greece.

Introduction
GH deficiency in adulthood is associated with increased cardiovascular risk, which is attributed to unfavorable changes in body composition and in metabolic parameters.
Aim
We evaluated haemodynamic, metabolic, inflammatory and coagulation indices that may contribute to the increased cardiovascular risk in GH deficient subjects.
Methods
Twenty-four patients diagnosed with GH deficiency (13 male), with a mean (S.D.) age of 54.3 (2.7), were compared to 15 healthy age, sex and BMI matched, controls. Anthropometric characteristics (BMI and waist-to-hip ratio (WHR)), blood pressure, basal GH, IGF-I, fasting glucose, fasting insulin, HbA1c, lipid levels, ApoA1, ApoB, hs-CRP, fibrinogen, PAI-1, t-PA and circulating thrombomodulin levels were measured in all study participants. Insulin resistance (IR) was calculated by HOMA and, in ten subjects who had undergone an oral glucose tolerance test, insulin sensitivity was also estimated using Matsuda index.
Results
Patients with GH deficiency exhibited a marginally increased WHR and had significantly higher fasting insulin levels, fasting glucose-to-insulin ratio, HbA1c, total-chol, LDL-chol and triglyceride levels, higher ApoB and lower HDL, compared to controls. IR did not differ by HOMA-IR, however, patients were less insulin sensitive than controls.
Fibrinogen levels and PAI-1 levels did not differ significantly, but t-PA was markedly increased compared to controls. Thrombomodulin levels were not affected.
Conclusions
A considerable number of risk factors including insulin sensitivity, lipid and lipoprotein levels and pro-thrombotic factors are affected in GH deficient adults. Studies addressing whether GH substitution results in decreased CVD morbidity and mortality are needed so therapy could be more vigorously implemented in such patients.
DOI: 10.1530/endoabs.37.EP797

EP798

Increased serum levels of the Wnt antagonist Dickkopf-1 (DKK1) and impaired trabecular bone mineral density using QCT scan in acromegalic patients

Elena Valassi[1], Iris Crespo[1], Anna Aulinas[1], Eulalia Urgell[2], Jorge Malouf[3], Jaume Llauger[4], Ana Maria Marin[3], Betina Biagetti[5] & Susan M Webb[1]
[1]II-B Sant Pau and Department of Internal Medicine/Endocrinology, Hospital Sant Pau, UAB and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBER-ER, Unidad 747), ISCIII, Barcelona, Spain; [2]Department of Biochemistry, Hospital Sant Pau, Barcelona, Spain; [3]Department of Internal Medicine, Mineral Metabolism Unit, Hospital Sant Pau, Barcelona, Spain; [4]Department of Radiology, Hospital Sant Pau, Barcelona, Spain; [5]Department of Endocrinology, Hospital Vall d'Hebron, UAB, Barcelona, Spain.

Introduction
Acromegaly is associated with increased bone turnover and skeletal fragility. Although the GH/IGF1 system plays an important role in bone homeostasis, effects of GH excess on the Wnt signalling pathway are to be determined. Bone quantitative CT (QCT) provides a volumetric, tridimensional measure of bone mass at the trabecular and cortical level.
Aim
i) To compare volumetric bone density (vBMD) using QCT in patients with acromegaly vs gender-, age-, and BMI-matched controls; ii) to correlate it with the levels of Wnt antagonists, dickkopf factor-1 (DKK1) and sclerostin (SOST), in the same subjects.
Methods
Thirty-one acromegalic patients (17 (55%) men; 18 (58%) with active disease; mean age 48.2±7.5 years (range 28–65 years)) and thirty-two age-, gender- and BMI-matched controls underwent QCT scan using Mindways Software. Serum concentrations of DKK1, SOST, ß-crosslaps, procollagen type-1 amino-terminal propeptid (P1NP) and osteocalcin were also measured.
Results
vBMD of cortical total hip (CTH vBMD) and trabecular total hip (TTH vBMD) were lower in acromegaly than controls (CTH vBMD, 776±199.4 vs 937±346.4 mg/cm^3; $P<0.05$ and TTH vBMD, 121.4±20.6 vs 142.8±22.8; $P<0.01$). P1NP levels were lower (41.7±20.5 vs 51±21.2 ng/ml, $P<0.05$), while DKK1 levels were higher (33.7±12.9 vs 26±14.8 pmol/l, $P<0.05$) in acromegaly patients compared to controls. No intergroup difference in ß-crosslaps, osteocalcin and SOST levels was observed. A negative correlation between DKK1 and TTH vBMD ($r=-0.382$, $P<0.01$) was observed. A positive correlation between P1NP, ß-crosslaps, and SOST with CTH vBMD ($r=0.34$, $r=0.27$, $r=0.26$, respectively, $P<0.05$) was also observed. After multiple regression analysis, DKK1 and disease duration were independent, negative predictors of TTH vBMD ($R^2=0.335$, $P<0.05$), whereas female gender was an independent, positive predictor of CTH vBMD ($R^2=0.156$, $P<0.05$).
Conclusions
Acromegaly patients exhibit low vBMD on QCT. The Wnt signalling antagonist DKK1 may contribute to the skeletal fragility described in acromegaly.
Supported by grants from FIS ISCIII PI 11/00001 and Fundación Merck Serono 2012.
Disclosure
Supported by grants from FIS ISCIII PI 11/00001 and Fundación Merck Serono 2012.
DOI: 10.1530/endoabs.37.EP798

EP799

Outstanding growth response to GH replacement therapy in three different cases of GH deficiency

Ljiljana Saranac[1], Zlatko Djuric[1], Ivana Markovic[2], Hristina Stamenkovic[1] & Dragoljub Lazarevic[1]
[1]Pediatric Clinic, Faculty of Medicine Nis, University of Nis, Nis, Serbia; [2]Institute of Radiology, University Clinical Centre Nis, Nis, Serbia.

Introduction
Growth response in GH deficient children during GH replacement therapy rarely fulfil our projections and patient's expectations. We here report three cases with outstanding growth response.

Case reports
First patient was diagnosed as gluten enteropathy in early childhood, but the diet didn't improve his growth. At age of 7 years the diagnosis of isolated GH deficiency (GHD) was established and GH substitution therapy introduced. Next 2 years his growth velocity increased to 10 cm/year. Routine head MRI revealed hypothalamic tumour. Severe growth failure in 8-years-old boy with history of purulent meningitis in toddler period and head trauma at age of 6. MRI discovered congenital pituitary abnormality (pituitary hypoplasia and ectopic posterior pituitary). Combined substitution therapy improved his height from −3S.D. to +0.67S.D. An empty sella syndrome was diagnosed in short obese boy with delayed puberty. At diagnosis his height of 148.8 cm was −1.88S.D. (P3). During 4 years of combined therapy he achieved height of 184 cm (P90), +1.28S.D.
Conclusion
Mechanisms of excellent growth response in these GH deficient children certainly include concomitant hypogonadism, but somatostatin deficiency may also be considered.

DOI: 10.1530/endoabs.37.EP799

EP800

Metformin-based oral antidiabetic therapy proved effective in hyperglycaemia associated with pasireotide in patients with acromegaly

Anna Maria Colao[1], Feng Gu[2], Monica R Gadelha[3], Aart J van der Lely[4], Maria Fleseriu[5], Vanessa Passos[6], Shoba Ravichandran[6], Yin Miao Chen[6] & Marcello D Bronstein[7]
[1]Dipartimento di Medicina Clinica e Chirurgia, Università Federico II di Napoli, Naples, Italy; [2]Key Laboratory of Endocrinology, Department of Endocrinology, Ministry of Health, Peking Union Medical College Hospital, Beijing, China; [3]Division of Endocrinology, Medical School and Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil; [4]Department of Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands; [5]Northwest Pituitary Center, Oregon Health and Science University, Portland, Oregon, USA; [6]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; [7]Neuroendocrine Unit, Division of Endocrinology and Metabolism, University of São Paulo Medical School, São Paulo, Brazil.

Introduction
High affinity binding of pasireotide for both sst_2 and sst_5 leads to its enhanced efficacy in treatment of acromegaly but results in decreased secretion of insulin, incretins (GLP-1 and GIP) and, to a lesser extent, glucagon. Metformin may be a good option in patients with acromegaly experiencing hyperglycaemia with pasireotide as it improves GLP-1 secretion. We analysed data from a 12-month, Phase III, randomised study in medically naïve patients with acromegaly to better understand the effects of antidiabetic agents used during pasireotide treatment.
Methods
Patients were randomised to pasireotide LAR 40 mg/28 days ($n=176$) or octreotide LAR 20 mg/28 days ($n=182$) for 12 months. Patients ($n=57$) randomised to pasireotide who were not receiving antidiabetic medication at baseline and who initiated such medication during the study were included in this analysis. Three groups were analysed: patients receiving i) metformin alone; ii) metformin + another oral antidiabetic (OAD); and iii) insulin ± OAD.
Results
Metformin was the most commonly initiated antidiabetic; metformin alone ($n=24$), metformin + another oral antidiabetic (OAD; $n=19$) and insulin ± OAD ($n=10$). Mean (S.D.) fasting plasma glucose (FPG) and HbA1c at baseline were 94.7 (13.0) mg/dl and 5.8% (0.4%) for metformin alone, 99.7 (12.8) mg/dl and 5.8% (0.4%) for metformin + another OAD, and 106.7 (19.7) mg/dl and 6.1% (0.5%) for insulin ± OAD. Mean (S.D.) FPG values at month 3 were 131.0 (37.2), 153.2 (41.6) and 170.0 (88.6) mg/dl, and at month 12 were 126.7 (17.4), 132.6 (25.0) and 137.1 (31.7) mg/dl in the three groups. HbA1c values were 6.6% (0.5%), 7.0% (1.0%) and 8.7% (1.9%) at month 3, and 6.6% (0.7%), 6.7% (0.6%) and 7.2% (1.2%) at month 12.
Conclusions
At month 12, patients treated with metformin monotherapy or in combination with OAD agents had a mean HbA1c that met the ADA/EASD goal of <7%. Metformin-based OAD therapy proved effective in hyperglycaemia associated with pasireotide in patients with acromegaly.
Disclosure
This work was supported by Novartis.

DOI: 10.1530/endoabs.37.EP800

EP801

Analysis of the aetiology of hypopituitarism: the results from double centre study

Mustafa Caliskan[1], Mehtap Navdar Basaran[2], Selvihan Beysel[1], Muyesser Sayki Arslan[1], Bekir Ucan[1], Mazhar Muslum Tuna[2], Erman Cakal[1], Dilek Sensoz Berker[2], Serdar Güler[2,3] & Tuncay Delibasi[1,4]
[1]Department of Endocrinology and Metabolism, Diskapi, Teaching and Research Hospital, Ankara, Turkey; [2]Department of Endocrinology and Metabolism, Numune Teaching and Research Hospital, Ankara, Turkey; [3]Faculty of Medicine, Hitit University, Corum, Turkey; [4]School of Medicine (Kastamonu), Hacettepe University, Ankara, Turkey.

Introduction
Hypopituitarism is commonly acquired in adult life and its main causes are pituitary tumors and/or their treatments, empty sella syndrome and etc.
Patients and methods
A double centre, cross-sectional database study was performed in Turkish population for last 10 years to investigate the etiology of hypopituitarism. One-hundred forty nine patients were included (53% female and 47% male) with a mean age of 47.9 ± 15.6 years (ranging from 19 to 83 years). Patients were classified by the causes of hypopituitarism as pituitary tumors (due to direct effect of the pituitary tumors and/or their treatments), extra-pituitary tumors, and non-tumoural causes.
Results
It was found that the most common etiology of pituitary dysfunction was due to non-tumoural causes (48.9%) among all patients (Table 1). According to the subgroup analysis of the causes of hypopituitarism, the most common cases with more than 10% frequencies were prolactinomas, non-secretory adenomas, idiopathic, and empty sella (Table 1). In terms of the type of hormonal deficiencies, FSH/LH deficiencies was the most common hormonal deficit (93.9%). In 70.4% of the patients, four anterior pituitary hormone deficiencies (FSH/LH, ACTH, TSH and GH) were present.

Table 1 Subgroup analysis of the frequencies of hypopituitarism in all patients (*n*, number of patients; (%), frequency).

Aetiology	*n* (%)
Pituitary adenomas	62 (41.6%)
Prolactinomas	13 (8.7%)
Acromegaly	2 (1.3%)
Cushing	3 (2%)
Gonadotrophinomas	1 (0.7%)
Thyrotropinomas	1 (0.7%)
Non-secretory adenomas	42 (28.2%)
Extra-pituitary tumors	13 (8.7%)
Non-tumoural causes	
Idiopathic	13 (8.7%)
Sheehan's syndrome	59 (39.6%)
Apoplexia	2 (1.3%)
Total	*n*=149

Note: Frequencies over 10% were represented in bold.

Conclusion
Although non-secretory pituitary adenomas were the most common cause of hypopituitarism in male patients, Sheehan's syndrome was the leading cause of hypopituitarism in female patients.

DOI: 10.1530/endoabs.37.EP801

EP802

A case of idiopathic granulomatous hypopysitis that was initially treated as a prolactinoma

Ismail Emre Arslan, Mehmet Muhittin Yalcin, Nuri Cakir, Alev Eroglu Altinova, Ilhan Yetkin, Müjde Aktürk, Fusun Balos Toruner & Metin Arslan
Endocrinology and Metabolism Department, Gazi University Faculty of Medicine, Ankara, Turkey.

Idiopathic granulomatous hypophysitis is a very rare inflammatory disease of the pituitary gland. Primary hypophysitis represents a difficult diagnostic challenge because it can imitate pituitary adenomas clinically and radiologically. The diagnosis is usually made histologically by hypophysectomy. We herein present a rare case of idiopathic granulomatous hypopysitis diagnosed primarily by pituitary biopsy.
Case
A 50-year-old female patient presented with headache, visual loss and menstrual irregularities over the preceding year. At her first visit at another hospital, TSH level was normal but prolactin level was high (PRL: 115 ng/ml). In her visual field examination, a near total defect on right eye and a peripheral visual field defect on left eye were detected. Pituitary MRI revealed a $17\times9\times12$ mm macroadenoma extending to optic chiasm. Cabergoline therapy was started. When she applied to our clinic 3 months later, pituitary MRI demonstrated a 6 mm microadenoma? and her vision complaints were disappeared; but hypocortisolism and secondary hypothyroidism were detected. Replacement therapies were started and cabergoline was stopped. This unexpected development of pituitary insufficiency necessitated a re-evaluation of MRI screenings. Because our decision was in favor of a possible hypophsitis, trans-sphenoidal pituitary biopsy was performed. Pituitary biopsy demonstrated non-necrotising granulomatous hypophysitis. Possible secondary causes were investigated and no evidence was found. The final diagnosis was idiopathic granulomatous hypophysitis. We decided to follow-up the patient and replacement therapies were continued. The patient had no further complaints.
Conclusion
Idiopathic granulomatous hypophysitis, which is a very rare disease, diagnosed by pituitary biopsy is the main characteristic of our remarkable case. In patients with pituitary insufficiency, considering hypophysitis is a crucial clinical decision especially if they have specific radiological findings because it is highly possible to treat these patients medically and avoid hypophysectomy.

DOI: 10.1530/endoabs.37.EP802

EP803

Transsphenoidal surgery of pituitary adenomas in 491 clinical cases: the retrospective single-centre study

Robertas Knispelis[1], Birutė Žilaitienė[1,2], Martyna Ramančiuckaitė[3], Rasa Verkauskienė[1], Kęstutis Šinkūnas[4], Rimantas Žalinkevičius[2] & Arimantas Tamašauskas[4,5]
[1]Department of Endocrinology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania; [2]Institute of Endocrinology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania; [3]Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania; [4]Department of Neurosurgery, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania; [5]Institute of Neurosciences, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania.

Introduction
The number of studies on the incidence and outcomes of surgical treatment for pituitary adenomas is still limited, despite that pituitary tumours are one of the most frequent intracranial tumours.
The aim of this study
To evaluate clinical features of transsphenoidaly operated pituitary adenomas (PA) and perioperative results of the treatment.
Materials and methods
This is a retrospective single institution study of 491 patients. Data were collected from medical records of patients operated during the period 1995–2014 at the Hospital of Lithuanian University of Health Sciences due to functioning and non-functioning micro or macroadenomas. The series consisted of 357 (64, 91%) female and 193 (35, 09%) male patients, with a mean age of 49.95 ± 16. 4 year (range 18–85 year).
Results
The study included 227 non-functioning and 264 functioning adenomas: 103 were GH, 122 prolactin (PRL), 32 ACTH and seve TSH secreting adenomas. Female patients were significantly younger than male patients ($P<0.$ 02). Gross total resection as ascertained by surgeon just after the operation was achieved in 92 (40.71%) cases of non-functioning adenomas, 62 (64.58%) cases of GH, 64 (55.17%) cases of PRL, 24 (85.71%) cases of ACTH, and 3 (42. 86%) cases of TSH secreting adenomas. According to the size the non-functioning tumours were significantly large than functioning adenomas. Tumour type and size directly influenced surgical outcome. The highest possibility for total tumour removal was detected in the case of ACTH secreting adenomas ($P<0.001$) and lowest in non-functioning adenomas ($P<0.001$). Surgical intraoperative rupture of membrane selle turcique and liquorrhea occurred in 16.51% and no major intraoperative complications were observed.
Conclusion
Our centre data confirm effectiveness and safety of transsphenoidal surgery for PA and the best prognosis for ACTH secreting PA.

DOI: 10.1530/endoabs.37.EP803

EP804

Pharmacokinetic and pharmacodynamic analyses of pasireotide LAR from a randomised, phase III study in patients with inadequately controlled acromegaly

Guoxiang Shen[1], Christelle Darstein[2], Karina Hermosillo Reséndiz[1] & Ke Hu[1]
[1]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; [2]Novartis Pharma AG, Basel, Switzerland.

Introduction
A 24-week, PhIII, randomised study (PAOLA) demonstrated superior efficacy of pasireotide long-acting release (PAS-LAR; 40 and 60 mg) vs continued treatment with octreotide LAR 30 mg or lanreotide Autogel 120 mg (15.4%, 20.0% vs 0%) at providing biochemical control (GH <2.5 μg/l and normalized IGF-1) in patients with acromegaly inadequately controlled on first-generation somatostatin analogues. Results from PK/PD analyses of PAS-LAR are reported here.
Methods
Relationship between PAS plasma concentration/efficacy endpoints (GH and IGF-1) and PAS exposure/safety (FPG, ECG, and liver function tests) were analysed. Dose-proportionality was explored and possible covariate effects were determined using linear mixed-effects models.
Results
A steady-state PAS concentration was achieved following three consecutive monthly injections. PAS exposures were approximately dose proportional for the tested dose range (40–60 mg). Gender, age, and baseline total bilirubin levels were statistically significant PK covariates for PAS concentration but without clinically significant impact. A clear exposure-response relationship was observed between PAS concentration and efficacy endpoints. Estimated maximum GH and IGF-1 suppression (mean $\pm$ S.E.M.) was $83.0\pm6.5\%$ and $67.1\pm5.8\%$, respectively. Estimated effective concentration of PAS to suppress GH to 2.5 μg/l was 12.3 ± 3.3 ng/ml; to suppress IGF-1 to $1\times$ULN required higher PAS concentration (42.3 ± 16.6 ng/ml). These results were aligned with clinical finding of higher response rate for GH vs. IGF-1 with 40 and 60 mg (40 mg: 35.4% vs 24.6%; 60 mg: 43.1% vs 26.2%). A 1.5-fold increase in PAS trough concentration (40–60 mg dose) was associated with a 54, 44, and 51% increase in the odds of GH+IGF-1, GH and IGF-1 responses, respectively; corresponding increase in the odds of having hyperglycaemia was only 36%.
Conclusions
A positive relationship between PAS exposure and efficacy supported the clinical observations of higher GH and IGF-1 response rates with higher dose (60 mg vs 40 mg). These results are aligned with the clinical findings of a positive benefit/risk profile for PAS-LAR treatment in this patient population.
Disclosure
This work was supported by Novartis.

DOI: 10.1530/endoabs.37.EP804

EP805

Pituitary apoplexy in GH-deficient adults treated with GH – a KIMS database retrospective study

Serban Radian[1], Peter J Jönsson[2], Cecilia Camacho-Hübner[3], Beverly M K Biller[4], Michael Buchfelder[5], Ann-Charlotte Åkerblad[3] & Márta Korbonits[1]
[1]William Harvey Research Institute, Queen Mary University of London, London, UK; [2]Pfizer Health AB, Sollentuna, Sweden; [3]Endocrine Care, Pfizer Inc., New York, New York, USA; [4]Massachusetts General Hospital, Boston, Massachusetts, USA; [5]Department of Neurosurgery, University of Erlangen-Nürnberg, Erlangen, Germany.

Background
Pituitary apoplexy (PitApo) has significant associated-morbidity and its management is not yet standardised.
Aim
To describe prevalence and characteristics of PitApo patients in GH deficient (GHD) patients compared with two control populations.
Patients and methods
Patients with 'infarction-apoplexy' GHD aetiology code were identified from Pfizer International Metabolic Database (KIMS). Baseline characteristics, GH dosage and 1-year response to GH replacement of PitApo patients were compared with non-functioning pituitary adenoma (NFPA, $n=3828$) and Sheehan's syndrome ($n=495$) control groups.
Results
We identified 151 PitApo patients (0.96% of 15.809 GHD patients), including eight PitApo reported as adverse events during KIMS. Median age at GHD diagnosis was lower in PitApo than NFPA (47.8 vs 51.8 years, $P<0.01$) and higher than Sheehan's patients (42.5 years, $P<0.001$). Gender distribution was similar in PitApo and NFPA groups (68.2% vs 60.8% males). There were no differences in dose between groups regardless of oestrogen use. The proportion of GH-naïve/semi-naïve patients with normal IGF-I after 1 year of GH replacement was similar between PitApo and NFPA (80.4% vs 82.5%) and lower in Sheehan's (57.8%, $P<0.0001$ vs PitApo). Median IGF-I SDS 1-year increase was similar in PitApo and NFPA (1.61 vs 1.92) and higher in Sheehan's (2.59, $P<0.05$ vs PitApo). Mean age/gender-adjusted serum total cholesterol decreased from baseline in PitApo (-0.76 mmol/l) vs NFPA (-0.32 mmol/l, $P<0.05$) and Sheehan's patients (-0.19 mmol/l, $P<0.05$), while LDL- and HDL-cholesterol changes did not differ. AGHDA-QoL-score reduction (indicating improved QoL) was similar in PitApo and NFPA (-4.33 vs -3.76 points) and higher than Sheehan's patients (-1.58 points, $P<0.01$ vs PitApo).
Conclusions
In this large cohort of patients with pituitary apoplexy, representing $<1\%$ of GHD patients overall, GH dose and treatment effects were comparable to NFPA controls, except for greater reductions in serum lipids, while Sheehan's controls attained normal IGF-I less frequently and their QoL improved less.
Disclosure
KIMS is sponsored by Pfizer, Inc. SR is a Marie Curie IEF postdoctoral fellowship recipient (grant no. 303006/2011).

DOI: 10.1530/endoabs.37.EP805

EP806

Psychological and neurocognitive evaluation in patients with pituitary adenoma

Elisa Sala[1,2], Barbara Zarino[3], Elena Malchiodi[1,2], Elisa Verrua[1,2], Giulia Carosi[1,2], Marco Locatelli[3], Paolo Rampini[3], Giorgio Carrabba[3], Anna Spada[1,2] & Giovanna Mantovani[1,2]
[1]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; [2]Endocrinology and Diabetology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [3]Unit of Neurosurgery, Fondazione IRCCS C Granda Ospedale Maggiore Policlinico, Milan, Italy.

Reduced health-related quality of life (HRQoL) and impairment in neurocognitive functions are a possible complaint in patients with pituitary adenoma. Psychiatric comorbidities in Cushing's disease are well known. However recent studies showed HRQoL reduction and psychiatric symptoms in patients with pituitary disease with or without hormonal excess. Aim of this study is to analyse HRQoL, psychiatric symptoms and neurocognitive functions in patients with pituitary adenomas, with either Cushing's disease or non-functioning pituitary adenoma (NPFA) before and after surgery. Through three validated questionnaires (SF-36, BDI-II, MMPI-II) and an interview with a psychologist, we assessed HRQoL, psychiatric symptoms and neurocognitive functions in 20 adult patients (age 49.6 ± 11.4, M/F = 12/8) harboring pituitary tumors (ten Cushing's disease and ten NPFA, macro/micro = 12/8). We conducted a baseline measurement before transphenoidal surgery as well as after 12 months. All Cushing's patients were in remission at the follow-up visit and pituitary deficiencies, when present, were adequately substituted. 20 healthy subjects, age- and sex-matched, were analysed as controls. Regarding HRQoL, patients with NFPA did not show significant differences compared to controls. On the contrary, patients with Cushing's disease had significantly lower HRQoL than NFPA and controls in all scales of SF-36 questionary, both at baseline and at follow-up. At follow-up NFPA patients showed an improvement in all scales while patients with Cushing improved only in role-physical and general health ones. Furthermore, BDI-II and MPI-II scales showed a significant increase of depression ($P=0.045$) and social inversion ($P=0.031$) in the Cushing's group. Lastly, both groups of patients, without any difference, showed a significant impairment in all neurocognitive functions tests at baseline compared to controls. At follow up, though, the difference had disappeared. According to the literature, this study confirms that Cushing's disease leads to a much larger impact on HRQoL and psychiatric comorbidities, with significant improvement after treatment but without a complete remission, probably due to irreversible changes in neural function. Interestingly, however, neurocognitive impairment is present and appears in all patients with pituitary tumors, independently of hormone secretion.

DOI: 10.1530/endoabs.37.EP806

EP807

Macroprolactinomas invasive and its response to treatment in women. Cali - Colombia cohort study

Paula Andrea Velásquez[1,2], Adriana Mayor[1,2] & Alin Abreu[1]
[1]Centro Medico Imbanaco, Cali, Valle del Cauca, Colombia; [2]Universidad Libre, Cali, Valle del Cauca, Colombia.

Background
Orolactin-producing tumours are the most frequent pituitary tumours, representing 40% of these tumours, with an annual incidence of 6–10 cases/million. $<10\%$ are macroprolactinomas, which vary by age and gender, with female to male ratio of 10:1, however, less diagnosed in this population group.
Objective
To describe clinical features and therapeutic response of 30 women with invasive macroprolactinoma.
Methods
Follow a cohort of 30 patients was performed, aged 18–47 years, in Imbanaco Endocrine Clinic Medical Center in Cali, Colombia, between 2002 and 2012. Demographic and clinical characteristics were analysed; signs, symptoms, hormone levels, surgery and complications. Univariate analysis to estimate proportions and measures of central tendency was performed according to the nature of the variable. Treatment success was defined as a decrease in time macroprolactinomas size, measured by NMR and decrease in serial serum prolactin. Parametric tests were used to compare serum prolactin and tumor size Fisher Snedecor's F was applied.
Results
The mean age was 35 years, and BMI 28. The symptoms were; 96.7% headache, menstrual disorders, 90, 80% hipopituarismo, visual disorder 76.7% decreased libido 73.3% Galactorrhoea/asthenia 70%, infertility 60, 30% unilateral amaurosis. Trans-cranial 16.7, 43.3% trans-sphenoidal surgery, 23% of patients started with bromocriptine, of these 10% used it as monotherapy, 13% remaining, cabergoline should start. 86% received only cabergoline. Regarding complications presented 20% empty sella, 3.3% rinoliquia. With statistically significant differences ($P<0.0001$) measurements at 6 and 12 months in the three diameters relative to the benchmark, like serum prolactin.
Conclusion
Interventions Patients were successful in 100% of cases.

DOI: 10.1530/endoabs.37.EP807

EP808

Trial design of phase IIIb, open-label, single arm study to evaluate efficacy and safety of pasireotide LAR in patients with inadequately-controlled acromegaly despite treatment with first-generation somatostatin analogues

Monica R Gadelha[1], Alberto M Pedroncelli[2], Albert Kandra[2], Karina Hermosillo Reséndiz[3] & Anna Maria Colao[4]
[1]Division of Endocrinology, Medical School and Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil; [2]Novartis Pharma AG, Basel, Switzerland; [3]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; [4]Dipartimento di Medicina Clinica e Chirurgia, Università Federico II di Napoli, Naples, Italy.

Introduction
The present study is designed to evaluate the efficacy and safety of pasireotide-long-acting release (LAR) in patients with acromegaly inadequately controlled after ≧3 mo treatment with the maximal approved doses of first-generation SSAs.
Methods
Phase IIIb, multicentre, single-arm, open-label study.
Patients
Adults (N∼112) with inadequately controlled acromegaly (mean GH > 1 μg/l and IGF-1 > 1.3xULN) despite receiving octreotide-LAR (30 mg/40 mg depending on the country) or lanreotide-ATG (120 mg) for ≧3 mo.
Design
Run-in phase (≧3 mos): patients on octreotide-LAR 30 mg despite the availability of the 40 mg dose at the time of screening will enter a run-in receiving three injections of octreotide-LAR 40 mg/28 day. Core phase (wk0-36): starting dose of pasireotide-LAR: 40 mg/28 day. GH and IGF-1 evaluated every 12 week and dose increased to 60 mg/28 day in uncontrolled patients (mean GH > 1.0 μg/l and/or IGF-1 > ULN) if no tolerability issues. Dose will remain unchanged in biochemically controlled patients. Dose decrease is permitted for safety reasons. During the extension phase (wk36–72), concomitant medications used to treat acromegaly are allowed if patients are uncontrolled on pasireotide 60 mg/28 day. Safety and tolerability will be assessed throughout the study.
Endpoints
Primary: proportion of patients with GH < 1 μg/l and IGF-1 < ULN at wk36; supporting analyses for primary endpoint will be performed in two patient subgroups by mean GH level at screening (GH: 1–2.5 μg/l, GH > 2.5 μg/l). Secondary: change in mean GH (five-point profile over a 2-h period), IGF-1xULN from study baseline to wk36; proportion of patients overall and by mean GH level at screening with GH < 1 μg/l and IGF-1 < ULN at wk12 and 24; GH < 1 μg/l alone, IGF-1 < ULN alone at wk12, 24 and 36, safety and health-related quality of life.
Conclusions
This study will evaluate efficacy and safety of pasireotide-LAR in patients with inadequately controlled acromegaly after ≧3 mo treatment with maximal approved doses of first-generation SSAs. In particular, a new patient population with GH 1–2.5 μg/l not studied in the PAOLA study will be evaluated.
Disclosure
This work was supported by Novartis.
DOI: 10.1530/endoabs.37.EP808

EP809

Thyrotropinoma – not just hyperthyroidism

Edyta Gurgul, Maria Gryczynska, Adam Maciejewski, Aleksandra Klimowicz, Dagny Lapinska & Marek Ruchala
Department of Endocrinology, Metabolism and Internal Medicine, Poznan University of Medical Sciences, Poznan, Poland.

Thyrotropinoma is a very rare cause of hyperthyroidism. In October 2014 a 41-year-old male patient was examined for anaemia and diarrhoea. Abdomen CT scan, gastroscopy, colonoscopy and parasite tests did not reveal any abnormalities. The patient had lost 18 kg 7 years ago and his weight had been stable since then (BMI 21.3 kg/m^2). The laboratory tests revealed high TSH, normal fT_4 and low cortisol level. The patient referred to our department presented with diarrhoea, velvet skin, loss of facial, chest, axillary and pubic hair; he admitted occasional heart palpitations. The results of insulin tolerance test showed secondary adrenal insufficiency. Other laboratory results were: TSH 13.56 μIU/ml (no increase in TRH stimulation test), fT_3 12.57 pmol/l, fT_4 55.55 pmol/l, low FSH, LH, DHEA-S, testosterone, GH and IGF-1 levels. Pituitary MRI demonstrated a solid intra- and suprasellar pituitary macroadenoma (25 mm) with sphenoid and cavernous sinus invasion and optic chiasm dislocation. Thyroid ultrasound showed low echogenicity of thyroid gland. Densitometry revealed osteoporosis. Diarrhoea resolved on gluten-free diet (suspected coeliac disease). ASCA antibodies were positive (suspected Crohn disease). The gastroenterological diagnosis has not been clearly stated. We introduced octreotide injections every 4 weeks, hormonal replacement and osteoporosis therapy. TSH, fT_3 and fT_4 still remain above upper limit of normal. Control pituitary MRI will be performed in February 2015 and the patient will be qualified for neurosurgical treatment. We conclude that clinical image of thyrotropinoma may be confusing due to coincident symptoms of pituitary deficiency and potential concomitant diseases. Optimal diagnosis and treatment require a multidisciplinary approach.

DOI: 10.1530/endoabs.37.EP809

EP810

Pasireotide long-acting release maintains biochemical control in patients with acromegaly: results from the extension of randomised, Phase III, PAOLA study

Anna Maria Colao[1], Marcello D Bronstein[2], Thierry Brue[3], Mihail Coculescu[4], Laura De Marinis[5], Maria Fleseriu[6], Mirtha A Guitelman[7], Vyacheslav Pronin[8], Gérald Raverot[9], Ilan Shimon[10], Juergen Fleck[11], Albert Kandra[11], Alberto M Pedroncelli[11] & Monica R Gadelha[12]
[1]Dipartimento di Medicina Clinica e Chirurgia, Università Federico II di Napoli, Naples, Italy; [2]Neuroendocrine Unit, Division of Endocrinology and Metabolism, University of São Paulo Medical School, São Paulo, Brazil; [3]Hôpital de la Timone, Centre National de la Recherche Scientifique, and Assistance Publique-Hôpitaux de Marseille, Aix-Marseille University, Marseille, France; [4]Academy of Medical Sciences of Romania University of Medicine and Pharmacy 'Carol Davila', National Institute of Endocrinology 'CI Parhon', Bucharest, Romania; [5]Università Cattolica del Sacro Cuore, Rome, Italy; [6]Northwest Pituitary Center, Oregon Health & Science University, Portland, Oregon, USA; [7]Hospital Carlos G Durand, Buenos Aires, Argentina; [8]IM Sechenov First Moscow State Medical University, Moscow, Russia; [9]Groupement Hospitalier Est, Hospices Civils de Lyon, Lyon, France; [10]Rabin Medical Center, and Sackler School of Medicine, Tel-Aviv University, Petah-Tiqva, Israel; [11]Novartis Pharma AG, Basel, Switzerland; [12]Division of Endocrinology, Medical School and Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil.

Introduction
The PAOLA study in patients with inadequately-controlled acromegaly ($n = 198$) demonstrated superior efficacy of pasireotide long-acting release (LAR; 40 mg/60 mg) in biochemical control (GH < 2.5 μg/l and normalized IGF-1) vs continued treatment with octreotide LAR 30 mg/lanreotide Autogel 120 mg (15.4% and 20.0% vs 0%). Here we report preliminary data from the extension phase of PAOLA at wk28.
Methods
Pasireotide-LAR (40 mg/60 mg) patients who were biochemically controlled at wk24 (core phase) continued with the same double-blind pasireotide LAR dose whereas uncontrolled patients started open-label pasireotide LAR 60 mg. Uncontrolled patients in the active-control group (octreotide LAR/lanreotide Autogel) patients crossed over to open-label pasireotide LAR 40 mg. Key efficacy endpoints at extension wk28 were i) proportion of patients with biochemical control ii) proportion of patients with GH < 2.5 μg/l or normal IGF-1 alone. Safety and tolerability were evaluated.
Results
A total of 173 patients entered the extension (pasireotide LAR 40 mg, $n = 57$; pasireotide LAR 60mg, $n = 54$ by randomised dose; crossover, $n = 62$). The preliminary analysis at wk28 in all patients achieving that time point, including early discontinuation showed that the proportion of patients with i) biochemical control was 18.4% (9/49), 33.3% (15/45), and 20.0% (10/50) ii) GH < 2.5 μg/l was 38.8% (19/49), 46.7% (21/45), and 42.0% (21/50); normal IGF-1 was 32.7% (16/49), 37.8% (17/45), and 24.0% (12/50), in the pasireotide LAR 40 mg-, pasireotide LAR 60 mg-, and crossover arm, respectively. Safety findings were consistent with the ones in the core phase; most common adverse events were hyperglycaemia, diabetes mellitus, cholelithiasis, and diarrhoea.
Conclusions
The preliminary data in patients achieving wk28 indicate that pasireotide LAR maintained biochemical control during the extension in patients with inadequately-controlled acromegaly; ∼20% of the active-control patients achieved biochemical control after crossing over to pasireotide in the extension.

No new safety signals were identified during the extension. These findings suggest that pasireotide LAR is a viable, long-term treatment option for patients with acromegaly.

Disclosure

This work was supported by Novartis.

DOI: 10.1530/endoabs.37.EP810

EP811

Ongoing, open-label, multicenter, expanded-access study demonstrating the safety and efficacy of pasireotide sc in patients with Cushing's disease

Luiz R Salgado[1], Günter K Stalla[2], Tania Longo Mazzuco[3], Eliza B Geer[4], Alberto M Pedroncelli[5], Moncy Ye[6], Albert Kandra[5] & Padiporn Limumpornpetch[7]

[1]University of São Paulo Medical School, São Paulo, Brazil; [2]Department of Internal Medicine, Endocrinology and Clinical Chemistry, Max Planck Institute of Psychiatry, Munich, Germany; [3]Health Sciences Centre, Universidade Estadual de Londrina, Londrina, Brazil; [4]Icahn School of Medicine at Mount Sinai, New York, New York, USA; [5]Novartis Pharma AG, Basel, Switzerland; [6]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; [7]Prince of Songkla University, Hat Yai, Thailand.

Background

Pasireotide (Signifor®), a multireceptor-targeted somatostatin analogue, was initially approved in Europe and the USA in 2012 for treating adult patients with Cushing's disease for whom surgery is not an option/has failed. This 'expanded-access' study allowed patients to receive pasireotide until regulatory approval was obtained in their country, and collected further safety/efficacy data. Here we report an interim analysis of this ongoing study.

Methods

Adult patients with confirmed Cushing's disease were enrolled; all had mean 24-h UFC > ULN. Patients initiated pasireotide at 600/900 μg sc bid; dose could be increased or decreased in 300 μg increments to a minimum of 300 μg for tolerability issues/sustained UFC normalization, or to a maximum of 900 μg. Patients remain in the study until pasireotide becomes commercially available in their country or 31/12/15, whichever occurs first. The primary objective was to assess the safety of pasireotide; changes in UFC and clinical signs/symptoms in patients with available measurements at weeks 12, 24 and 48 were evaluated as secondary objectives.

Results

As of 31/7/14, 97 patients enrolled (mean age 42.2 ± 12.8 years). Median exposure to pasireotide was 23.6 weeks (range 1–131). 22 patients (22.7%) are still on study and 29 (29.9%) have completed; 46 (47.4%) discontinued: primary reasons were AEs ($n=16$), unsatisfactory therapeutic effect ($n=13$), consent withdrawal ($n=13$) and other ($n=4$). Most AEs were mild/moderate; most common: nausea ($n=48$; 49.5%), diarrhoea ($n=46$; 47.4%), hyperglycaemia ($n=38$; 39.2%). At weeks 12, 24 and 48: 35/71 (49.3%; 95% CI 37.2–61.4), 24/49 (49.0%; 34.4–63.7) and 11/27 (40.7%; 22.4–61.2) patients had UFC < ULN; 40/71 (56.3%; 44.1–68.1), 26/49 (53.1%; 38.3–67.5) and 11/27 (40.7%; 22.4–61.2) had UFC decrease ≥50% from baseline. Improvements were observed in signs/symptoms, including facial rubor, supraclavicular/dorsal fat pads, striae and bruising.

Conclusions

This study provides further evidence that pasireotide effectively decreases UFC levels and improves clinical signs/symptoms, with a generally favourable safety profile, in patients with Cushing's disease.

Disclosure

This work was supported by Novartis.

DOI: 10.1530/endoabs.37.EP811

EP812

Is there a role for the 24 h GH profile in the assessment of acromegaly?

Robert D'arcy, Patrick Bell, Hamish Courtney, David McCance, Steven Hunter & Karen Mullan

Regional Centre for Endocrinology and Diabetes, Royal Victoria Hospital, Belfast, UK.

Recent Endocrine Society guidelines advocate IGF-1, random GH and nadir GH after oral glucose tolerance test (OGTT) for assessment in acromegaly. In our regional centre the 24 h GH profile has also been used partly because of changing IGF-1 assay methodology but also because of concerns that IGF-1 may not adequately reflect partial therapeutic success. We evaluated 58 GH profiles in 35 patients from April 2008 to November 2012 when both GH and IGF-1 assays remained unchanged. Samples were drawn every 2 h from 0800 to 0800 (13 time points) and matched with OGTT and IGF-1. In 20 patients paired profiles were available pre and 3 month postoperatively. Correlation between the mean 13 and five point (0800–1600) profile was strong ($r=0.98$, $P<0.01$). Correlations between the mean 13 point profile and nadir GH on OGTT and IGF-1 were also moderate-strong ($r=0.96$, $P<0.01$ and $r=0.65$, $P<0.01$ respectively). Preoperatively there was full concordance between 0800 GH and IgF-1 and GH profiles. Six patients had discordant results postoperatively (high 0800 GH ≥1 μg/l; normal IGF-1). Three of these had a 13 point mean of <1 μg/l. In the five patients with high 0800 GH (≥20 μg/l) preoperatively reductions in GH postoperatively were considerable (88–99%) and in one patient mean GH was <1 μg/l. In these five patients IGF-1 was not normalised being modestly reduced (34-64%) and in one patient, elevated by 33%.

Conclusions

GH profiling is not necessary in assessing the majority of patients with acromegaly if there is confidence in the local IGF-1 assay. When undertaken, a five point profile is adequate. In patients with high 0800 GH values profiling may more adequately reflect therapeutic effect than IGF-1. Further work is needed to explore the role of the GH profile in stratifying patients with discordant IGF-1 and GH results postoperatively.

DOI: 10.1530/endoabs.37.EP812

EP813

Cone beam computed tomography reveals altered trabecular bone structure in acromegaly

Andrea Giustina[1], Gherardo Mazziotti[1], Michele Maddalo[2], Filippo Maffezzoni[1], Stefano Frara[1], Ivan Zorza[2], Pierantonio Soldini[2], Francesco Doglietto[3] & Roberto Maroldi[2]

[1]Endocrinology, University of Brescia, Brescia, Italy; [2]Radiology, University of Brescia, Brescia, Italy; [3]Neurosurgery, University of Brescia, Brescia, Italy.

Over the last years, there has been evidence that acromegaly may cause skeletal fragility with high risk of vertebral fractures. The diagnostic approach to this complication is still a matter of uncertainty, since DXA measurement of bone mineral density (BMD) does not provide reliable information on fracture risk in acromegaly. The cone beam computed tomography (CBCT) technique offers three-dimensional images for the radiographed area with the advantage to use non-dedicated equipments as compared to the peripheral Quantitative Computed Tomography. The aim of this study was to investigate whether a non-dedicated CBCT system may provide information on the skeletal abnormalities caused by acromegaly. Twenty-two patients with acromegaly (12 females, ten males; mean age 62 years, range 25–72) and 16 healthy control subjects (six females and ten males; mean age 59 years, range 25–68) were studied using high resolution CBCT system (Newtom 5G; QR, Verona, Italy) at the distal radius. All acromegaly patients were also evaluated for DXA BMD at lumbar spine, total hip, femoral neck and distal radius. Patients with acromegaly showed lower trabecular bone volume fraction (BV/TV) ($P=0.001$) and mean trabecular thickness (Th.mean) ($P=0.001$) and greater mean trabecular separation (Sp.mean) ($P=0.01$), without significant difference in cortical thickness ($P=0.47$) as compared to the control subjects. In acromegaly patients, the duration of active disease significantly correlated with BV/TV (r: −0.69; $P=0.001$), Th.mean (r: −0.46; $P=0.05$) and Sp.mean (r: 0.47; $P=0.04$). In acromegaly patients, the BMD at distal radius significantly correlated with cortical thickness ($r=0.56$; $P=0.007$), whereas the BMD at either skeletal site was not significantly correlated with the trabecular parameters. In acromegaly patients, the distal radius CBCT reveals significant alterations of physiological trabecular bone structure which may be responsible for their high risk of fragility fractures even in the presence of normal BMD.

DOI: 10.1530/endoabs.37.EP813

EP814

Cabergoline test as a predictor for long term therapy management of hyperprolactinaemia

Andra Caragheorgheopol[2], Iuliana Busila[1], Ruxandra Dobrescu[2], Adriana Gogoi[2] & Corin Badiu[1,2]
[1]'Carol Davila' University of Medicine and Pharmacy, Bucharest, Romania; [2]'C.I.Parhon' National Institute of Endocrinology, Bucharest, Romania.

Objective
To determine if the response to one single dose of 0.5 mg cabergoline (CAB) can be used as predictor for choosing personalized therapy of hyperprolactinaemia. Although CAB is a selective, long half-life D2-receptor agonist some patients proved to be resistant with minimum to no response in serum prolactin and tumour shrinkage, even after a few months of treatment.
Patients and methods
A dose of 0.5 mg CAB was administered orally to a number of 53 naive patients, in a prospective interventional study. Based on hyperprolactinaemia two groups were selected: the first group of 38 patients with prolactinoma and a second group of 15 patients with other causes of hyperprolactinaemia, who served as control. In the prolactinoma group all cases were prospectively evaluated, starting a maintenance phase with 2–3 mg cabergoline twice a week for at least 6 months. This second phase allowed us to divide the prolactinoma group into sensitive and resistant cases: 31 proved to be sensitive and seven resistant to CAB, when comparing the results of serum prolactin dosage and tumour shrinkage on CT/MRI scan. The main test consists of a first phase when a single dose of CAB is administered and the serum prolactin is measured at basal, 12 and 48 h comparing these results. For a more complete understanding and analysis of linkage mechanism the plasma CAB levels were also measured using a mass-spectrometry based method. The instrumental analysis was performed on a HPLC tandem mass-spectrometer in the multiple-reaction monitoring method (MRM).
Results
CAB determined prolactin decrease in both sensitive and resistant cases but with a significant difference. In sensitive prolactinoma the decrease showed to be from 2781 to 1099 ng/ml at 12 h (which means almost with 60%, $P=0.001$), 1075.1 ng/ml at 24 h and 843.63 at 48 h. The highest decrease was registered at 12 h after CAB administration. In resistant prolactinomas, the decrease went from 3675.7 ng/ml basal value to 2043 ng/ml at 12 h, 1679.71 at 24 h and 1586.6 ng/ml at 48 h (which means lower than 45% in the first 12 h). In the control group the decrease was also much smaller. In the follow up time: one patient with small response at CAB test proved to be long-time therapy responsive and another one with prolactin decrease on CAB test, proved to develop partial response in long time treatment. Meanwhile, CAB pharmacokinetics showed the highest value at 12 h, which was 9.50 pg/ml, with 6.44 pg/ml at 24 h and 4.73 pg/ml at 48 h.
Conclusions
CAB test can provide information about the sensitivity to treatment for a better future management and good results, which is allowing patients to receive personalized therapy in adapted method and time duration. Anyway, further studies with larger study population should be done in order to completely understand all possible determinants of a better or a more accurate therapy response.

DOI: 10.1530/endoabs.37.EP814

EP815

Renal function in acromegaly

Christine Pichl, Sylvère Störmann, Matthias Pichler & Jochen Schopohl
Klinikum der Universität München, Medizinische Klinik und Poliklinik IV
Mailing adress: Ziemsenstraße 1, Munich, Germany.

Introduction
Acromegaly is a rare disease resulting from GH excess mostly due to pituitary adenomas. It is associated with changes of most organ systems and multiple comorbidities. The impact of GH and IGF-I excess on renal function in acromegaly is unclear.
Methods
We investigated 66 acromegalic patients from our outpatient clinic (32 female, 34 male, mean age 61.5 ± 12.9 years, women 10 years older than men). The renal function was assessed by blood and urine tests, ultrasound and blood-gas analysis.
Results
38 patients were considered biochemically controlled according to latest recommendations on criteria for cure of acromegaly (IGF-I in age- and gender-specific reference range, random basal GH <1 ng/ml). 12 patients were partially controlled (IGF-I up to 1.3 times elevated), 16 biochemically active. 61% of the patients have hypertension (68% of the controlled, 75% of the partially and 31% of the uncontrolled patients), 21% of the patients presented with diabetes mellitus, 11% have both. The distribution between the sexes was balanced. According to the Cystatin C formula ($GFR(CysC) = 77.24 \times \text{Cystatin C}^{-1,2623}$) 39 patients (59%) presented with reduced glomerular filtration rate (GFR $<$ 90 ml/min). 50% of the patients have a chronic kidney disease stage 2 (GFR 60–89 ml/min), 9% stage 3 (GFR 30–59 ml/min). Despite their higher age the median GFR of the female patients is 4 ml/min higher (82.4 vs 86.4 ml/min). The median GFR of hypertonic patients is 21.6 ml/min lower than in patients without hypertension (80.8 vs 102.4 ml/min). There is no significant difference between the GFR of controlled, partially and not controlled patients in our patients (81.9 vs 89.5 vs 84.1 ml/min).
Conclusion
We found a reduced renal function (GFR $<$90 ml/min) in 59% of acromegalic patients. The disease activity has no effect on GFR as determined by Cystatin C formula.

DOI: 10.1530/endoabs.37.EP815

EP816

Successful treatment of huge pituitary macroadenoma secreting TSH and GH

Agnieszka Adamska, Agnieszka Zapora-Kurel & Maria Gorska
Department of the Endocrinology, Diabetology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland.

Introduction
The mixed tumor which secretes an excess of both GH and TSH causing acromegaly and hyperthyroidism is rare. The main problem is the late diagnosis, especially in men, even 10 years after the occurrence of the first symptoms.
Case report
A 53-year-old men, was admitted to the our department, with complaints of excessive sweating and enlargement of the hands. His medical history included arterial hypertension. Past medical history revealed thyroidectomy 20 years ago. Physical examination showed typical signs of acromegaly and nodules in both lobes of the thyroid gland. Performed laboratory test revealed elevated plasma concentrations of the PRL levels: 79.52 (0–29 ng/ml), IGF1: 593 (87–267 ng/ml) and lack of the suppression of GH after 75 g glucose (6.67 ng/ml). Additionally, we observed central hyperthyroidism: fT_4: 3.09 (0.7–1.48 ng/ml), fT_3: 17.49 (1.45–3.48 pg/ml) and TSH level: 6.095 (0.35–4.94 mU/ml) with normal anti-TPO: 0.4 (0–4.1 ng/dl). Diagnosis was confirmed by dynamic testing with TRH. An ultrasound scan of the thyroid showed a multinodular goitre. MRI revealed a large pituitary macroadenoma measuring $5 \times 6 \times 6$ cm with left cavernous and sphenoid sinus invasion, with compression of the optic chiasm, the third ventricle as well as the brainstem. Firstly, patient was treated with thiamazol, octreotide LAR and bromocriptine during 6 months. Then, he proceeded twice to the transsphenoidal resection of the pituitary macroadenoma with consecutive partial reduction of the tumor mass. After neurosurgery laboratory signs of hyperthyroidism resolved but serum GH was still elevated. Currently, the patient is under octreotide LAR therapy.
Conclusions
We presented an unusual case with a huge pituitary macroadenoma secreting TSH and GH who was successfully treated with transsphenoidal adenomectomy. This case showed that despite of symptoms and size of mixed tumour, diagnosis could be missed for the long time. On the other hand, the proper preparation for surgery, lets avoid the complications during the perioperative period.

DOI: 10.1530/endoabs.37.EP816

EP817

Management of Cushing's disease: single centre experience

Mirsala Solak[1], Ivana Kraljevic[1], Tina Dusek[1], Ante Melada[2], Marcel Marjanovic Kavanagh[3], Vjerislav Peterkovic[2], David Ozretic[4] & Darko Kastelan[1]
[1]Department of Endocrinology, Center of Neuroendocrinology Zagreb, Zagreb, Croatia; [2]Department of Neurosurgery, Center of Neuroendocrinology Zagreb, Zagreb, Croatia; [3]Department of Otorinolaringology, Zagreb, Croatia; [4]Department of Radiology, University Hospital Center, Zagreb, Croatia, Zagerb, Croatia.

Introduction
Cushing's disease (CD) is an uncommon condition of excess endogenous glucocorticoids caused by ACTH secreting pituitary corticotroph adenoma.

The purpose of this study is to review therapeutic outcomes and comorbidity of patients with CD in a single centre.
Methods
We conducted a retrospective study of 33 patients with CD undergoing transsphenoidal surgery from January 2007 to February 2014. (27 female and six male, median age 38 years, range 18–71 years). The diagnosis of Cushing's syndrome was established on the basis of the patient's history, characteristic clinical features and laboratory data, including elevated 24-h urinary free cortisol (UFC) level, lack of serum cortisol suppression after suppression tests (1-mg overnight dexamethasone suppression test and/or 2 mg-2 days dexamethasone suppression test) and elevated midnight cortisol level. In 28/33 patients tumor was visualised on MR of sellar region, while in five it was diagnosed using an inferior petrosal sinus sampling.
Results
Ten patients had macroadenoma, the remaining 23 had microadenoma. Twenty-one patients (63.6%) had hypertension, 17 (51.5%) dyslipidemia, while 7 (21.2%) had type 2 diabetes or Impaired Glucose Tolerance. Median follow-up period was 58.3 months. Remission after transsphenoidal surgery was achieved in 78.8% of patients, while seven patients failed to achieve disease remission. They were treated with second-line treatment modalities (second operation, radiotherapy, bilateral adrenalectomy and/or ketoconazole). One patient rejected all treatment modalities after surgery.
Conclusion
Cumulative remission after all treatment modalities was achieved in 93.9% patients. Two female patients had recurrence of hypercortisolism. The results of our Centre are comparable to leading centers in the world.

DOI: 10.1530/endoabs.37.EP817

EP818

Post-operative serum cortisol levels as predictors of recurrence in Cushing's disease

Diana Martins[1], Daniela Guelho[1], Isabel Paiva[1], Carla Baptista[1], Nuno Vicente[1], Luís Cardoso[1], Diana Oliveira[1], Margarida Balsa[2] & Francisco Carrilho[1]
[1]Endocrinology, Diabetes and Metabolism Department of Coimbra Hospital and University Centre, Coimbra, Portugal; [2]Endocrinology, Diabetes and Nutrition Department of Baixo Vouga Hospital Centre, Aveiro, Portugal.

Introduction
Cushing's disease (CD) is characterized by increased secretion of ACTH often as a result of a pituitary adenoma. The surgical success rates after transsphenoidal pituitary surgery (TSS) range from 53 to 96% in different centres. Postoperative cortisol levels have been proposed as the standard criteria for prediction of surgical remission however, this variable is subject of a variety of interferences.
Objectives
Evaluate the potential of post-transsphenoidal pituitary surgery cortisol levels to predict surgical remission and recurrence of CD.
Methods
Retrospective cohort study of patients with clinical and biochemical diagnosis of CD, submitted to TSS and followed in our centre between 1977 and 2013 ($n=84$). Patients who lost follow-up or with insufficient data on their personal records were excluded ($n=51$). Statistical analysis: SPSS(21).
Results
Thirty three patients, 29 (87.9%) women, with a median age of 33 years were included. All patients underwent TSS as first treatment option and were followed postoperatively during a median period of 8 (1–28) years. Eighteen (57.8%) patients achieved disease remission after the first treatment, 11 (33.3%) presented recurrence and 3 (9.1%) patients had persistent disease. Post-operative morning cortisol levels were lower in cured patients than in patients with recurrent or persistent disease (5.3 vs 8.1 vs 16.1 μg/dl, respectively, $P<0.05$). It was also observed an inverse correlation between morning serum cortisol levels and time free of disease ($r=-0.81$, $P<0.01$). We verified that cortisol levels at midnight were significantly different in the immediate post-operative evaluation than in the evaluation at 1 month and a half (5.30 ± 7.58 μg/dl vs 4.20 ± 6.84 μg/dl, $P<0.01$) . However both evaluations of midnight cortisol correlated significantly with the number of recurrences ($P<0.01$).
Conclusions
Serum cortisol levels can be a predictor of recurrence risk and also influence in time free of disease. However, midnight serum cortisol levels can fluctuate significantly in time.

DOI: 10.1530/endoabs.37.EP818

EP819

Endocrine manifestations of Langerhans cell histiocytosis

Luis Cardoso[1], Leonor Gomes[1,2], Dírcea Rodrigues[1,2], Carolina Moreno[1,2], Daniela Guelho[1], Nuno Vicente[1], Margarida Balsa[3], Diana Martins[1], Diana Oliveira[1] & Francisco Carrilho[1]
[1]Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; [2]Faculty of Medicine, University of Coimbra, Coimbra, Portugal; [3]Department of Endocrinology, Centro Hospitalar do Baixo Vouga, Aveiro, Portugal.

Introduction
Langerhans cell histiocytosis (LCH) is a rare disorder characterized by proliferation/accumulation of cells phenotypically similar to skin Langerhans cells. Clinical presentation and aggressiveness are very heterogeneous, from benign to disseminated forms that cause significant morbi-mortality, particularly endocrine failures.
Case 1: A 15-year-old Caucasian woman presented with a 14-month history of headaches, secondary amenorrhea. She reported polyuria and polydipsia in the last 2 years. Secondary evaluation revealed hypogonadism hypogonadotrophic, central hypothyroidism, and a 1 cm suprasellar lesion. Surgical excision of the lesion was performed, though histologic examination was inconclusive, and pan-hypopituitarism developed after surgery. Radiotherapy was prescribed due to persistent disease. Two years later, biopsy of recurrent vulvar ulcers revealed HCL. Subsequent studies showed active disease in the vulvar region, thyroid and hypothalamic–pituitary axis, which remitted after several cycles of vulvar radiotherapy, and systemic chemotherapy with prednisolone, methotrexate, and vinblastine (PDN/MTX/VBA).
Case 2: A 37-year-old Caucasian man presented with a 6-month history of otalgy, otorrhea, weight loss, and skin brown maculo-papular rash. He reported polyuria and polydipsia in the previous five years. Secondary evaluation revealed pan-hypopituitarism and a suprasellar mass of 2 cm. Temporal bone biopsy revealed HCL. Patient was treated.
Case 3: A 60-year-old Caucasian woman presented with 6-month history of jaw pain and weight loss. Secondary evaluation revealed polyostotic HCL and the patient was treated with zoledronic acid. Three years later the patient complained of headaches, polyuria, and polydipsia. Complimentary evaluation revealed diabetes insipidus, hypogonadism hypogonadotrophic, central hypothyroidism, and pituitary stalk enlargement. All patients required permanent hormonal substitution for the failed HPA sectors.
Conclusion
All cases described had hypothalamo-pituitary axis involvement with pituitary failure. The dominant manifestation was diabetes insipidus. If not treated promptly LCH may have a considerable morbi-mortality with permanent endocrine failures, that require proper hormonal substitution. Relapses may occur and appropriate follow-up is recommended.

DOI: 10.1530/endoabs.37.EP819

EP820

High BMI in female patients with prolactinomas

Irena Ilovayskaya, Alexander Dreval, Yulia Krivosheeva, Irina Chikh & Galina Stashuk
Moscow Regional Research and Clinical Institute N.A. M.F. Vladimirskiy, Moscow, Russia.

We analysed BMI of 270 female patients: 148 with hyperprolactinaemia (non-tumoural hyperprolactinaemia, $n=46$; microadenomas, $n=56$; and macroadenomas, $n=46$), 55 with isolated central hypogonadism, 67 with hypopituitarism. Additionally, 53 healthy women of reproductive age and 51 postmenopausal women were examined. In patients with hyperprolactinaemia median prolactin levels were 1547 (1124; 2185), 1490 (1050; 2280), and 3100 (1790; 18840) mE/l, accordingly ($P=0.002$). Median BMI in hyperprolactinaemic women was elevated (25 (23; 34.5) kg/m^2) but this parameter varied in dependence of hyperprolactinaemia type: BMI was 22.5 (20; 23) kg/m^2 in non-tumoural hyperprolactinaemia, 23 (22; 34.5) kg/m^2 – in microprolactinomas and 32 (26; 35) kg/m^2 – in macroprolactinomas ($P=0.023$). There was no significant correlation between BMI and prolactin levels; however, there was a positive correlation between BMI and prolactinoma volume ($r=0.49$, $P=0.015$). BMI in women with nontumoral hyperprolactinaemia did not differ from healthy women (21 (20; 23.5) kg/m^2, $P=0.8$) and women with isolated central hypogonadism (22.2 (20; 23.8) kg/m^2, $P=0.6$). BMI in women with microprolactinomas was significantly higher than in healthy women and in non-tumoral hyperprolactinaemia ($P=0.03$) however was comparable with hypopituitary patients (24 (22.7; 27.3) kg/m^2, $P=0.33$) and postmenopausal women (24.4 (23.2; 27.1) kg/m^2, $P=0.35$). The highest BMI was noted in patients with macroprolactinomas and

it was significantly greater than BMI in other hyperprolactinaemic and non-hyperprolactinaemic subgroups ($P<0.001$ for all). Thus, we conclude that hyperprolactinaemia *per se* is not a risk factor for obesity in women. Prolactin-secreting pituitary lesions lead to the higher rate of increased BMI, and macroprolactinomas are more powerful risk factor for obesity than physiological menopause or hypopituitarism.

DOI: 10.1530/endoabs.37.EP820

EP821

Study of the prevalence and related factors in the withdrawal of medical treatment macroprolactinomas

Lorena Suarez Gutierrez[1], Maria Galiana Rodriguez Caballero[2], Cecilia Sanchez Ragnarson[2], Nuria Valdes García[2], Laura Cacho García[2] & Edelmiro Menendez Torre[2]
[1]Hospital of Cabueñes, Gijón, Spain; [2]University Hospital of Asturias, Oviedo, Spain.

Introduction
The prolactinoma is the most common functioning pituitary tumour. There are few long-term studies on the optimal duration of treatment with dopamine agonists prolactinoma to ensure healing without recurrence after stopping the medication and do not provide a consensus on it or on withdrawal criteria treatment.
Objectives
To establish the prevalence of withdrawal of treatment macroprolactinomas and evaluate criteria prolactinoma cure medical treatment and analysing the possible factors involved.
Methods
Retrospective study of 77 patients diagnosed and treated for prolactinoma in the Service Endocrinology of University Hospital of Asturias, from 1982 to 2012. Only 56 patients were treated exclusively with dopamine agonists and the rest were excluded. Of these 40 patients continue with treatment and 16 patients were withdrawn from treatment (eight men and eight women) after verifying the suppression of prolactin (PRL) levels and the disappearance of the pituitary mass. In 28.6% removal treatment and 44.6% could meet criteria.
Results
The withdrawal of treatment was on average after 11.01 ± 7.36años (2.26–26.8) normalization of prolactin. After removal medical treatment was resumed in 50% patients at 1, 6, 12, and 60 months respectively. The cause of restarting treatment was in all the elevation of plasma PRL levels. No significant differences between withdrawal and not withdrawn for age, sex, prolactin levels presuspension, initial tumour size, type of response, and dose of agonist withdrawal.
Conclusions
Following the withdrawal of treatment with dopamine agonists after an average of 10 years under normal PRL and almost complete tumour shrinkage was reintroduce 50% of the patients in our series. Re-introduction why treatment was in all cases prolactin elevation. No tumour regrowth in any of the control images. We observed no relation to either the initial size nor PRL figures presuspension or other predictors by the limited sample size.

DOI: 10.1530/endoabs.37.EP821

EP822

The effect of gonadotropin treatment on insulin resistance and cardiovascular risk factors in patients with idiopathic hypogonadotropic hypogonadism

Yasin Simsek[1], Kenan Guclu[2], Gulden Baskol[2] & Fahri Bayram[1]
[1]Department of Endocrinology, Erciyes University, Kayseri, Turkey; [2]Department of Biochemistry and Clinical Biochemistry, Erciyes University, Kayseri, Turkey.

Introduction
Idiopathic hypogonadotropic hypogonadism (IHH) is a rare disorder characterised by delayed or absent sexual maturation and infertility associated with inappropriately low gonadotropin and sex steroid levels. Insulin resistance (IR) is defined as an impaired biologic response to both endogenous and exogenous insulin. IR is a common precursor to the development of glucose intolerance, including diabetes, hypertension, and cardiovascular disease. Dyslipidaemia, apolipoprotein B-100 (ApoB-100), homocysteine, ApoA1, and high sensitive C-reactive protein (hsCRP) are another risk factors on coronary artery disease. We aimed to to look at the role of gonadotropin replacement treatment in development of IR and other cardiovascular risk factors in patients with IHH.
Materials and methods
Twenty-four male patients with untreated IHH were enrolled into the study. IR was calculated by the homeostasis model assessment of IR (HOMA-IR) form. Plasma glucose, insulin, hsCRP, homocysteine, ApoA1, ApoB-100, LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-K), triglyceride (TG), total cholesterol (TC) levels were measured in fasting blood samples, and biochemical and hormonal analyses were performed for all study participants before and after treatment.
Results
Before and after gonadotropin replacement, HOMA-IR were 3.12 ± 1.44 and 1.98 ± 1.48; LDL-C levels were 110.8 ± 33.7 and 91.8 ± 27.6 mg/dl respectively. There was a statistically significant difference between HOMA-IR ($P=0.001$) and LDL-C levels ($P=0.004$). However, there was no statistically significant differences among other parameters ($P>0.05$).
Conclusions
Gonadotropin replacement can significantly improve patients' insulin sensitivity and decrease serum LDL-C levels. Therefore, gonadotropin replacement may prevent developing diabetes mellitus and cardiovascular diseases in future.

DOI: 10.1530/endoabs.37.EP822

EP823

Clinical features and treatment outcomes of resistant acromegaly patients: a single-centre study

Özgür Demir, Asena Gökçay Canpolat, Berna Imge Aydoğan, Çağlar Keskin, Şule Canlar, Mustafa Şahin, Rifat Emral, Sevim Güllü, Vedia Tonyukuk Gedik, Ali Riza Uysal & Demet Çorapçioğlu
Department of Endocrinology and Matabolism, Ankara University Faculty of Medicine, Ankara, Turkey.

Introduction
Disease control in acromegaly can be achieved by surgery, medical treatment, and radiotherapy either alone or in combination. The acromegaly patients whom tumour shrinkage cannot be provided or growth hormone levels do not decrease under multiple treatment modalities are designated as resistant acromegaly. We aimed in our study to evaluate the clinical features of resistant acromegaly patients and determine their responds to different treatment modalities.
Methods and results
47 acromegaly patients were enrolled between 2007 and 2015 in this study. 18 of patients (ten men and eight women) were accepted as resistant acromegaly according to their clinical course. The median age, median tumour size and mean IGF1 levels at diagnosis were found 36.5 (28–62), 21 mm (12–70), and 1184 ± 567 ng/ml respectively. The mean numbers of their operation and radiation were found 2 (0–3) and 1 (0–1). Of these 18 procedures, 15 were transsphenoidal procedures and three involved transfrontal surgery. Histological evaluation revealed exhibition of sparse granular staining in eight patients. Long acting somatostatin analogue therapy dose was increased in three patients. Cabergoline (0.5–2 mg/week) and pegvisomant therapy were added to their somatostatin analogue therapy in five and ten patients respectively. The mean follow-up was 18 ± 4 months. There were no difference found between these tree treatment modalities. IGF1 normalisation was achieved overall in 94% of resistant acromegaly patients.
Discussion
Resistance to traditional treatment options in acromegaly represents 25% of whole cases. We found a similar ratio as 39% in our case series. Resistant group was found to be diagnosed at younger age, with greater dimensions of tumour and found to have more sparse granular staining compatible with literature. We could not find any differences between IGF1 levels. It is also a debate as whether which treatment option is suitable for resistant patients.

DOI: 10.1530/endoabs.37.EP823

EP824

A rare case of GH deficiency: mucolipidoses type II/III

Elena Braha[1,2], Ioana Armasu[2], Cristina Rusu[1], Daniela Raileanu[3], Adina Manolachie[2], Georgiana Constantinescu[2], Mirela Puiu[2], Roxana Stefan[2] & Carmen Vulpoi[2]
[1]Department of Genetics, University of Medicine and Pharmacy 'Gr.T. Popa', Iasi, Romania; [2]Department of Endocrinology, University of Medicine and Pharmacy 'Gr.T. Popa', Iasi, Romania; [3]County Hospital, Botosani, Romania.

Introduction
Mucolipidoses II/III (ML) are rare autosomal recessive lysosomal storage disorders (incidence: 1/325 000 live births). They have overlapping clinical phenotypes with mucopolysaccharidosis disorders and include growth retardation, facial dysmorphism, skeletal abnormalities, respiratory and heart diseases, hepatosplenomegaly and abdominal hernias. There is no specific treatment and the management has been limited to supportive care.
Case presentation
A Manolachie aged 18, boy of an young non-consanguineous apparently healthy couple, in evidence of the Genetics Department for mucopolysaccharidosis type I, was first addressed to the Endocrinology Department at the age of 14 years 4 months for investigations of growth retardation. The clinical examination revealed short stature (-4 S.D.), 'elf' facies, limited extension and abduction of the upper limbs with bilateral tendon retraction of the fingers and also in the radiocarpal and elbow joints, decreased mobility of the spine and waddling walk with wide support base; no signs of pubertal onset. Wrist radiography revealed delayed bone age of $\sim$6 years. Somatotropic axis investigations revealed low IGF1 (62.4 ng/ml, $n=220$–972, GH $=0.42$ ng/ml, without stimulation at the arginine test: GH $=2.75$ ng/ml) pleading for GH deficiency. Since there were not known contraindications, GH replacement therapy was started with an initial dose of 0.035 mg/kg per day and biannual reassessments were performed. After 4 years of treatment the medium growth rate was 0.42 cm/month and no side effects were reported. The last wrist radiography revealed delayed bone age (11 years and 6 months) permitting treatment continuation. At the last evaluation the enzymes α-iduronidase, iduronate-2-sulfatase, arylsulfatase B, β-galactosidase could be assessed and were indicative of MLV II/III.
Conclusions
Corroborating the clinical phenotype, biological data and evolution, this case can be included in MLV III. We haven't found in the literature any case of MLV III treated with GH replacement therapy. In our case the treatment was effective and improved the patient's quality of life.

DOI: 10.1530/endoabs.37.EP824

EP825

Performance of early cortisol measurements post transphenoidal surgery in predicting ACTH sufficiency as assessed by dynamic testing

Christopher McAlpine[1], Aikaterini Theodoraki[1], Anne Dawnay[1], Neil Dorward[2], Joan Grieve[2] & Stephanie Baldeweg[1]
[1]University London College Hospital, London, UK; [2]National Hospital For Neurology and Neurosurgery, London, UK.

Background
After pituitary surgery patients require HPA axis assessment, that is achieved with postoperative cortisol measurements and, in selected patients whose post-operative cortisol measurements are inconclusive, with the insulin tolerance test (ITT) and the glucagon stimulation test (GST).
Aim
We aimed to assess the performance of the day 2/3 post-operative cortisol in predicting the HPA axis sufficiency as assessed by the ITT and the GST.
Methods
Retrospective review of all pituitary surgical records done in 2004–2014 in a tertiary centre.
Results
71 patients met the inclusion criteria, out of which 41 (57.7%) had an ITT and 30 (42.3%) a GST. 0900 h cortisol measurements on day 2/3 postoperatively did not differ between the patients having an ITT or a GST (353 ± 188 vs 348 ± 194, P 0.85). Peak cortisol measurements post dynamic testing were 549 ± 218 for ITT and 458 ± 241 for GST. ROC curve analysis showed that day 2/3 postoperative cortisol of $\leq$142 nmol/l was 100% (84–100%) sensitive in detecting patients that would fail the ITT, with 31% (14–56%) specificity, and a cut-off of $\geq$470 nmol/l was 94% (69–100%) specific in identifying patients with ACTH sufficiency with 32% (17–52%) sensitivity. When applying the same cut-offs in GST, a day 2/3 cortisol of $\leq$142 nmol/l was 93% (62–100%) sensitive in detecting patients that would fail the GST, with 28% (12–51%) specificity, and a cut-off of $\geq$470 nmol/l was only 78% (54–91%) specific in identifying patients with ACTH sufficiency with 50% (26–75%) sensitivity.
Conclusion
After pituitary surgery a day 2/3 postoperative cortisol of $\leq$142 nmol/l detects all patients with ACTH insufficiency, and a cortisol of 470 nmol/l excludes ACTH insufficiency.

DOI: 10.1530/endoabs.37.EP825

EP826

Acquired male hypogonadotropic hypogonadism in a type 2 diabetes patient revealing empty sella

Hela Marmouch[1,2], Tasnim Slim[1], Fadia Boubaker[1], Sondes Arfa[1], Sameh Graja[1,2], Hanene Sayadi[1,2], Manel Jmal[1,2] & Ines Khochtali[1,2]
[1]Department of Internal Medicine–Endocrinology, Monastir, Tunisia; [2]Faculty of Medicine, Monastir, Tunisia.

Introduction
Empty sella in male patients is a very rare situation. It could be diagnosis in acquired male hypogonadotropic hypogonadism or hypopituitarism.
Case report
A 55-year-old type 2 diabetes male was referred to our hospital with erectile dysfunction (ED). He has three children. His secondary sex characteristics, sexual function, and ejaculation were previously normal but for the last 3 years he had ED. His genital stage was Tanner V, and pubic hair stage was Tanner III. There were no varicoceles. The diabetes was poorly controlled (Hb1Ac $=9\%$). His hormonal data were LH 1.1 mIU/ml (normal: 2–8 mIU/ml), FSH 1.8 mIU/ml (2–12 mIU/ml), testosterone 1.2 ng/ml (3–7 ng/ml), and FT_4 13 pmol/l (10–20 pmol/l). The rate of PSA was normal. Magnetic resonance imaging of the head revealed slight depression of the diaphragma sellae, indicating an 'empty sella'. We diagnosed acquired hypogonadtropic hypogonadism related empty sella. A replacement androgen therapy was introduced. Twelve months after hormone replacement therapy, the ED wasn't disappear but the quality of life of this patient was better.
Discussion
ED is common in type 2 diabetes men poorly controlled. It may reveal endocrine dysfunction such as acquired functional male hypogonadotropic hypogonadism (MHH). Pituitary MRI is frequently normal.
Conclusion
In this observation, we report a common situation in type 2 diabetes patient which revealed a rare case of acquired MHH due to empty sella. Pituitary MRI is interesting in acquired MHH and can reveal multiples others endocrine deficiency.

DOI: 10.1530/endoabs.37.EP826

EP827

Early postoperative basal cortisol level as good predictor of hypothalamic–pituitary–adrenal axis function after transsphenoidal surgery for pituitary tumours

Tanja Skoric Polovina[2], Mirsala Solak[2], Ivana Kraljevic[2], Tina Dusek[1,2], Maja Baretic[2] & Darko Kastelan[1,2]
[1]Zagreb University School of Medicine, Zagreb, Croatia; [2]University Hospital Center Zagreb, Zagreb, Croatia.

Accurate assessment of the hypothalamic–pituitary–adrenal (HPA) axis is important for the appropriate management of patients with pituitary tumours after transsphenoidal surgery. The aim of our study was to evaluate the clinical relevance of the early postoperative basal cortisol level in assessing postoperative HPA axis function. We performed a retrospective analysis of 68 patients (male:female $=36:32$, age 59.5 years, range 21–77) treated by transsphenoidal surgery between September 2011 and October 2014 at our centre of neuroendocrinology (44 nonfunctioning pituitary adenoma, 15 somatotrophinomas, five symptomatic Rathke's cleft cysts bigger than 15 mm, three craniopharyngeomas, and one macroprolactinoma resistant to medical therapy). Patients with Cushing's disease were excluded as well as patients with preoperative HPA insufficiency. Early postoperative basal cortisol levels (measured on the second postoperative day) and a Synacthen stimulation test (performed 10–12 weeks after the operation with a peak cortisol level of $>$550 nmol/l considered as normal response) were analyzed to assess HPA axis function during follow-up. We found that basal cortisol level of $\geq$249.5 nmol/l measured on the second day after the operation is a sensitive and accurate predictor of normal postoperative HPA axis function, with a sensitivity of 87.8%, and a specificity of 52.6%. Our data suggest that early postoperative cortisol level of $\geq$249.5 nmol/l predicts distant, normal postoperative HPA axis function following transsphenoidal surgery.

DOI: 10.1530/endoabs.37.EP827

EP828

A case of adrenal crisis secondary to ipilimumab-induced autoimmune hypophysitis

Anna Todd & Athinyaa Thiraviaraj
Altnagelvin Area Hospital, Londonderry, UK.

A 42-year-old man undergoing ipilimumab therapy for stage IV metastatic melanoma presented after his third dose with vomiting, abdominal pain, hypotension, and pyrexia. He was treated as a presumed line sepsis. Four days prior to admission, thyroid function test showed T_4 of 7.9 pmol/l and TSH 0.02 mU/l and he was treated with levothyroxine. A pituitary profile was carried out on admission and the results were as follows, cortisol was 24 nmol/l, testosterone <0.2 nmol/l, LH 1.5 U/l, FSH 5.1 U/l, and prolactin 135 mU/l. Pituitary profile had been normal at start of treatment. Acting on the above results he was commenced on hydrocortisone and clinically improved rapidly. CT brain found no abnormality in the pituitary region. MRI showed an atrophic pituitary with homogenous enhancement, normal stalk and a preserved posterior pituitary bright spot. Given the finding of new pan-hypopituitarism he was treated as an adrenal crisis secondary to ipilimumab related autoimmune hypophysitis, despite lack of pituitary or stalk enlargement on imaging. There is no consensus in the literature on how to manage ipilimumab related hypophysitis. Some centres advocate high dose i.v. or oral steroids, while other centres feel that steroids do not affect the outcome. Our patient was treated with high dose i.v. methylprednisolone therapy followed by a rapidly reducing dose of oral prednisolone therapy. He had symptomatic improvement from this, but continues to demonstrate pan-hypopituitarism at assessment 3 months after treatment. This case describes adrenal crisis secondary to immune related hypophysitis caused by ipilimumab and management of it with i.v. methylprednisolone. Frequency of immunotherapy for treating solid organ tumours is increasing and clinicians need to be aware of these life threatening side effects and their treatment.

DOI: 10.1530/endoabs.37.EP828

EP829

Glucose homeostasis alterations in Cushing's disease: epidemiology, anthropometric assessment and the role of family history of type 2 diabetes

Przemyslaw Witek[1], Joanna Witek[2,3], Grzegorz Zielinski[3], Marlena Blazik[4] & Grzegorz Kaminski[1]
[1]Department of Endocrinology and Isotope Therapy, Military Institute of Medicine, Warsaw, Poland; [2]Diabetes Outpatient Clinic, Institute of the Mother and Child, Warsaw, Poland; [3]Department of Neurosurgery, Military Institute of Medicine, Warsaw, Poland; [4]Paediatric Outpatient Clinic, Warsaw, Poland.

Introduction
Cushing's disease (CD) leads to glucose homeostasis alterations, obesity, unfavorable changes in body composition and cardiovascular complications.
Aim of study
i) Prospective evaluation of the frequency of pre-diabetes and diabetes. ii) Assessment of insulin resistance (IR) indices in CD. iii) Analysis of the influence of family history of type 2 diabetes (T2D) on the anthropometry in CD.
Methods
The study group included 47 patients with CD (37 women and ten men, aged 43.1 ± 14.6). Waist and hip circumferences, BMI, and body fat content were recorded. Glucose and insulin levels during an oral glucose tolerance test (OGTT) were assessed. HOMA-IR, QUICKI, and Matsuda indices were calculated. Patients previously diagnosed with diabetes were examined exclusively for fasting glucose and HbA1c.
Results
Sixteen patients (34%) had diabetes, another 18 (38.3%) had pre-diabetes. Hypertension was confirmed in 37 patients (78.7%). Mean total fat content was 34.52 ± 10.64 kg and trunk fat was 17.49 ± 5.18 kg. Mean BMI was 30.9 ± 6.6 kg/m^2. Obesity was confirmed in 23 patients (48.9%) and overweight in 17 (36.2%). In patients with hypertension trunk fat was higher than in the normotensive group (18.38 ± 4.87 kg vs 14.25 ± 5.2 kg, $P<0.05$). Positive family history of T2D was found in 15 patients (32%). It was associated with a greater hip circumference (114.37 ± 17.84 cm vs 102.81 ± 9.6 cm, $P<0.05$) compared to those without T2D in the family history. Matsuda and QUICKI indices were higher in patients without concomitant glucose homeostasis alterations than in patients with pre-diabetes (4.01 ± 2.04 vs 2.08 ± 0.92, $P=0.001$ and 0.338 ± 0.034 vs 0.311 ± 0.024, $P=0.01$ respectively). There was no significant difference with regards to HOMA-IR (2.78 ± 1.44 vs 5.33 ± 4.82, $P=0.08$).
Conclusions
i) Glucose homeostasis alterations were observed in 70% of patients with CD. ii) We confirmed the association between the presence of arterial hypertension and trunk fat content. iii) The family history of T2D may be associated with a higher risk of obesity in CD. iv) Matsuda index contrary to HOMA-IR may be a more sensitive marker of IR in CD.
Disclosure
This work was supported by the grant of Military Institute of Medicine No. 1/8807(258)/2013.

DOI: 10.1530/endoabs.37.EP829

EP830

Cushing's disease: reversibility of glucose homeostasis alterations and improvement in insulin resistance indices following a successful, transsphenoidal surgery

Joanna Witek[1,2], Przemyslaw Witek[3], Grzegorz Zielinski[2], Marlena Blazik[4] & Grzegorz Kaminski[3]
[1]Diabetes Outpatient Clinic, Institute of the Mother and Child, Warsaw, Poland; [2]Department of Neurosurgery, Military Institute of Medicine, Warsaw, Poland; [3]Department of Endocrinology and Isotope Therapy, Military Institute of Medicine, Warsaw, Poland; [4]Paediatric Outpatient Clinic, Warsaw, Poland.

Introduction
Cortisol excess in Cushing's disease (CD) leads to glucose homeostasis alterations and increased cardiovascular risk.
Aim of the study
i) To assess the reversibility of glucose homeostasis alterations and dynamics of inflammatory and coagulation parameters after the successful transsphenoidal surgery (TSS) for CD. ii) Analysis of the early improvement in insulin resistance (IR) indices following TSS.
Methods
The group consisted of 26 patients (22 women and four men; aged 41.5 ± 13.3) with early remission of CD. Anthropometric parameters, glucose, and insulin levels during an oral glucose tolerance test (OGTT), HbA1c, hsCRP, fibrinogen, and D-dimers were assessed prior to, and 3 months after TSS. HOMA-IR, QUICKI, and Matsuda indices were calculated. Patients previously diagnosed with diabetes were assessed exclusively for fasting glucose and HbA1c.
Results
Four patients (15.4%) had been diagnosed with diabetes prior to CD confirmation. Five patients (19.2%) were diagnosed with diabetes based on OGTT results prior to surgery. Ten patients (38.5%) were diagnosed with impaired glucose tolerance. A significant decrease in OGTT parameters was confirmed: fasting blood glucose (95.9 ± 17.4 mg/dl vs 83.8 ± 13.4 mg/dl, $P<0.05$), mean blood glucose (155.4 ± 34.1 mg/dl vs 117.3 ± 21.6 mg/dl, $P<0.0001$), 60-min glucose (182.6 ± 45 mg/dl vs 135.8 ± 30.6 mg/dl, $P<0.001$), and 120-min glucose (161.5 ± 52.2 mg/dl vs 118.7 ± 33.9 mg/dl, $P<0.05$). The Matsuda index and QUICKI improved significantly (2.8 ± 1.8 vs 5.2 ± 3.6, $P<0.01$ and 0.32 ± 0.03 vs 0.35 ± 0.04, $P<0.05$ respectively). Three months after TSS decrease in BMI and reduction in waist and hip circumference were not significant. No differences were observed with regards to mean, fasting and 120-min insulin levels, HbA1c, HOMA-IR, hsCRP, D-dimers, and fibrinogen.
Conclusions
i) Three months following successful TSS for CD significant decrease in fasting, mean and 120-min OGTT glucose levels could already be seen. ii) The Matsuda index and QUICKI might be more sensitive IR indices in the early postoperative period compared to commonly used HOMA-IR. iii) To demonstrate improvement in anthropometric parameters, insulin levels during OGTT, inflammatory and coagulation parameters, a longer follow-up may be required.
Disclosure
The studies were partly supported by the grant of Military Institute of Medicine No. 1/8807(258)/2013.

DOI: 10.1530/endoabs.37.EP830

EP831

Post-operative ACTH and cortisol values and its correlation with long-term clinical features in Cushing's disease

Celia Rios Perez[1], Carmen Fajardo Montañana[1,2], Pablo Abellan Galiana[3,4], Pedro Riesgo Suarez[1], Jose Gomez Vela[1], Carlos Messeguer Escriva[1], Enrique Molla Olmos[1], Gisela Alaman Laguarda[1], Jose Luis Llacer Ortega[1] & Jose Piquer Belloch[1,2]
[1]Facultad de Medicina, Universidad Católica San Vicente Martir (UCV), Valencia, Spain; [2]Hospital Universitario de La Ribera, Alzira, Spain; [3]Hospital General Universitario, Castellon, Spain; [4]Facultad de Medicina, Universidad CEU Cardenal Herrera, Castellon, Spain.

Introduction
It has been described that early post-operative cortisol value <2 μg/dl might predict long-term remission while ACTH value has been less described.
Objective
To study early post-operative ACTH and cortisol levels in Cushing's disease patients as predictor factor of long-term remission.
Patients
61 consecutive patients (12 men/49 women), mean age 42.6 years (17–86 years) undergoing transphenoidal hypophysectomy for Cushing's disease from 2005 to 2014 in our hospital. Mean followed-up period 32.1 ± 23.6 months. Post-operative ACTH and cortisol were measured, without replacement treatment, every 4–6 h. We study early clinical features, hormone values, radiological images, histological and surgical findings and clinical outcome at the end of the follow-up period.
Results
54 patients (88.5%) met clinical criteria for remission (97.3% micro, 77.7% macro, and 66.6% without MRI). Total surgical adenoma removal was performed in 86% patients (except six partial resections and two hemihypophysectomy based on cathetherism result). After initial surgery, post-operative serum cortisol was undetectable (<2 μg/dl) in 40 patients (27 micro, ten macro, and three without MRI). Recurrence was observed in 12/54 (22.2%) of the patients, 19.3 ± 12.2 months after achieving disease-remission, with a higher ACTH nadir value after surgery (25.9 ± 15.6 pg/ml vs 9.9 ± 8.8 pg/ml; $P=0.005$) and a long time to achieve cortisol nadir <2 μg/dl (58.9 ± 24.4 months vs 40 ± 20.6 months; $P=0.044$), while there were not differences in cortisol nadir value, adenoma size, sex, and age between recurrence and remission patients.
Conclusions
Intraoperative identification and selective removal of the pituitary adenoma, even if they were not identified by preoperative MRI, correlated with initial clinical remission in our patients. Early post-operative cortisol and ACTH measurements (without hormonal therapy replacement) have a prognostic value. Cortisol level <2 μg/dl has a curative predictive value in patients with Cushing's disease while a higher ACTH value after surgery and a long time to achieve cortisol nadir can predict recurrence.

DOI: 10.1530/endoabs.37.EP831

EP832

Who needs pre-operative medical blockade for Cushing's disease?

Elisabeth Trapp, Julia Prague & Ben Whitelaw
King's College Hospital, London, UK.

The definitive treatment for Cushing's disease is curative surgery. Patients with severe disease burden will likely require pre-operative medical blockade to reduce the risk of peri- and post-operative complications. The threshold for deciding when to medically block excess cortisol is currently based on clinical judgment. Expert centres may use a different criteria to determine this. There is no widely adopted tool for evaluating the clinical severity of Cushing's disease.
Methods
We retrospectively identified 30 consecutive patients diagnosed with Cushing's disease who proceeded to transphenoidal surgery. Using the Sonino Cushing's severity index (CSI) we then retrospectively calculated each patient's clinical severity disease score by reviewing their medical notes.
Results
All 30 patients (100%) had sufficient information documented in their medical records to enable retrospective calculation of their CSI score (mean 5.8, range 0–10). Twenty-three percent (7/30) received pre-operative medical blockade. Of the seven patients who received blockade: five received metyrapone alone, one ketoconazole alone, and one received both metyrapone and ketoconazole. The mean duration of blockade was 14 weeks (range 2–30). The mean CSI of patients deemed to need pre-operative blockade was 7.9 compared to 5.2 in the patients who were deemed to not need prior optimisation ($P=0.017$). Only one of 18 patients (6%) with a CSI <7 was prescribed blockade. Six of the 12 patients (50%) with a SCI in the range ≥ 7 received medical blockade.
Conclusion
We report our recent practice which shows that patients with a CSI of <7 are very unlikely to require pre-operative medical blockade. However, CSI of 7–9 will often be an indication for blockade and CSI of ≥ 10 is highly likely to be an indication. As such this scoring system with these associated cut off values could easily be utilised in clinical practice to guide medical decision making and facilitate comparison outcomes between expert centres.

DOI: 10.1530/endoabs.37.EP832

Thyroid cancer

EP833

Sarcoidosis in a 53-year-old women followed for a refractory thyroid carcinoma: a misleading association

Philippe Thuillier, Nathalie Roudaut, Véronique Kerlan & Sonnet Emmanuel
CHRU BREST, Brest, France.

Sarcoïdosis is a relatively frequent systemic disease of unknown origin. Prevalence is about 4.7–64 in 100 000. We report the case of a 53-year-old woman followed in our institution since 2007 for a thyroid carcinoma. In 2010, she was diagnosed refractory thyroid carcinoma because of a high thyroglobulin assay (477 μg/l) without uptake on post-therapeutic (^{131}I) whole body scan. Thereafter, the story is marked by the appearance in 2011 of multiple cervical and mediastinal lymph nodes, pulmonary and bones lesions. Bones lesions were treated with surgery, additive radiation therapy and cementoplasty. Between 2011 and 2013, we observed pulmonaries lesions progression with an aspect of lymphangitic carcinomatosis. In early 2013, morphologic evaluation showed the appearance of multiple lymph nodes (hepatic hilum, inguinal bilaterally). Biologically, we noted a slight increase of thyroglobulin assay (711 μg/l). In May 2013, a tyrosine kinase inhibitor, Sorafenib 400 mg twice a day was started. Six months later, a therapeutic evaluation was performed. TEP–TDM showed a majoration of mediastinal, abdominal, and inguinal lymph nodes and pulmonary lesions uptakes (SUV max 12.8) and an intense splenic uptake. Biologically, thyroglobulin assay remained paradoxically stable (673 μg/l). Because of this atypical presentation for a thyroid metastasis disease (lymphangitic carcinomatosis, unusual splenic metastasis, and stable thyroglobulin assay) and past history of breast cancer, a biopsy of a left inguinal lymph node was finally performed. Histological analysis demonstrated an aspect of epitheloid cell granuloma reaction with no caseous necrosis. This aspect was consistent with the diagnosis of sarcoidosis. Sorafenib was discontinued and a corticotherapy was started, enabling an improvement of respiratory symptoms. TEP–TDM performed in April 2014 showed a disappearance of all lymph nodes, pulmonaries, and splenic uptakes. In conclusion, sarcoidosis should be considered in case of atypical thyroid metastatic disease, when presentation is consistent with this diagnosis.

DOI: 10.1530/endoabs.37.EP833

EP834

What are the delays in the management of thyroid cancer?

Dave F N Fung & Sebastian Aspinall
North Tyneside General Hospital, Newcastle, UK.

Introduction
This audit aims to evidence the compliance of our practice with guidelines on the management of thyroid cancer. This may help to promote quality improvement in areas where there is substandard clinical care and service provision.
Method
In this retrospective study, patients diagnosed with thyroid cancers at our unit between 2009 and 2014 were identified. Electronic records were examined to establish the dates of referral, clinic attendance, investigations, and treatment, allowing us to determine whether patients received timely assessment and treatment. The quality of our ultrasound reporting and inadequacies of cytological assessment were also documented. A comparison was made against standards as proposed by the British Thyroid Association.
Results
There were 37 cases of thyroid cancer. 18 patients presented with a symptomatic thyroid nodule, five as incidental radiological findings and 14 as incidental pathological findings. Of the 23 cases with suspicious thyroid nodules, 11 were

not seen in clinic within 2 weeks of referral and eight did not have first definitive treatment within 62 days. The mean time to their diagnostic fine-needle aspiration (FNA) was 32 days. Of the 30 ultrasound scans completed, 23 were performed prior to Endocrine Clinic. However, none of these reports included all suggested features for risk stratifying thyroid nodules. Of the 41 FNA performed, 12 yielded inadequate specimens. The mean time to a repeat FNA was 104 days.
Conclusion
There was a considerable proportion of inadequate FNA specimens and thyroid nodules were poorly classified on ultrasound reporting. This may be why there was a significant lag period to a diagnostic FNA with subsequent delays to management. We recommend ultrasound assessment for risk stratification of all thyroid nodules and that this is clearly reported. In addition, any inadequate specimens should have a repeat FNA urgently under ultrasound guidance.

DOI: 10.1530/endoabs.37.EP834

EP835

Ectopic ACTH secretion by metastatic medullary thyroid carcinoma

Faiza Qari
King Abdulaziz University, Jeddah, Saudi Arabia.

A 45-year-old male known case of sporadic medullary thyroid carcinoma with metastasis to lymph nodes and bone. He underwent total thyroidectomy and modified neck dissection and external radiation in 2003. He was admitted with MTC which was progressive with rising calcitonin from 9000 to 40 000 μg/l. He underwent urgent tracheostomy and assessed by ENT and found to have bilateral vocal cord palsy. Patient improved; however on further assessment he was found to have severe proximal muscle weakness and he is unable to stand from sitting position.

Hormonal assay	Patient
ACTH	61 pg/ml
Serum cortisol (am)	↑ 1089 nmol/l
Serum cortisol (pm)	↑ 1004 nmol/l
24 h U for free cortisol	562 nmol/l
Dexamethasone suppression test	No suppression

Radiological investigations
Pituitary MRI is normal. MRI spine thoracic show multiple bony mets with no cord compression. Bilateral inferior petrosal sinus sampling (IPSS) for ACTH levels. CRH + vasopressin stimulation: ACTH 117 – max response 127 nmol/-cortisol 1003 – max response 1045 nmol/l.
Discussion
The diagnosis is ACTH-dependant Cushing's syndrome. The most likely the underlining cause of this condition in this patient is due to ectopic ACTH secretion by metastatic medullary thyroid carcinoma.

DOI: 10.1530/endoabs.37.EP835

EP836

Thyroid malignancy concurrent with hyperthyroidism: variations with thyroid status and age

Nadeesha Nawarathna[1], Navam Kumarasinghe[1], Deepthika Chandrasekara[1], Shamali Balasooriya[2], Aruna Shaminda[1] & Ranjith Senevirathne[1]
[1]Teaching Hospital, Kandy, Sri Lanka; [2]University of Peradeniya, Peradeniya, Sri Lanka.

Introduction
Thyroid malignancy associated with hyperthyroidism is considered rare. Retrospective studies have shown the incidence of thyroid malignancy in hyperthyroid patients to be low (0.7–8.5%). To assess the clinical relevance of this association, thyroid status in a cohort of patients with thyroid malignancy were analysed.
Method
Thyroid malignancies diagnosed histologically in 56 patients, over a 18-month period beginning from April 2013, in a single surgical unit at Teaching Hospital Kandy were included. Preoperative patient details and progression of thyroid status were asessed with TSH, free thyroxine, and free triiodothyronine levels.
Results
Amongst 56 patients papillary carcinoma was diagnosed in 44 (78.6%), follicular carcinomas in 7 (12.5%), and 5 (8.9%) with medullary and anaplastic carcinomas. 12 (21.4%) were males and 44 (78.6%) were females. 20 (35.7%) were <40 years, 29 (51.8%) were between 40 and 59 years and 7 (12.5%) were above 59 years. Cross tabulation of type of carcinoma with gender revealed likelihood ratio of 6.908, significance $P=0.032$. Biochemically 12 (21.4%) were hyperthyroid. Out of them 5 (41.7%) had primary hyperthyroidism and 7 (58.3%) had secondary hyperthyroidism. Mean age of euthyroid patients was 43.77 years (S.D. 10.574) and hyperthyroid patients was 53.25 years (S.D. 16.057). Independent samples *t*-test is -2.446, two tailed significance $P=0.018$. When cross tabulate thyroid status with age group likelihood ratio was 9.640, significance $P=0.008$.
Conclusion
Papillary carcinoma is seen more among females. Among the patients with thyroid carcinomas, those with biochemically proven hyperthyroidism were more among the older age group than those who were euthyroid. Hence, careful evaluation of elderly hyperthyroid patients to select the most suitable therapeutic approach is justified.

DOI: 10.1530/endoabs.37.EP836

EP837

Comparable ablation outcome between second and third ablation doses of 30 mCi radioactive iodine (^{131}I) in patients with papillary thyroid cancer

Khaled Salman[1], Safwan Zatary[2], Shereen Wagieh[3], Maha Abd-El Kareem[4], Yasser Mohammad[4], Sherif Abd-El Razek[5] & Manal Al-Ezzi[3]
[1]Nuclear Medicine Department, King Abdulla Medical City (KAMC), Mekka, Saudi Arabia; [2]Endocrinology Department, King Abdulla Medical City (KAMC), Mekka, Saudi Arabia; [3]Nuclear Medicine Department, King Abdulla Medical City (KAMC), Jeddah, Saudi Arabia; [4]Nuclear Medicine Department, Cairo University Hospital, Cairo, Egypt; [5]Assuit University Hospital, Assuit, Egypt.

Introduction
Complete ablation of residual thyroid tissue in patients with papillary thyroid cancer decreases locoregional recurrence, distant metastases and cancer death. No single group achieved 100% complete ablation post first ablation dose with variable successful complete ablation rate. In patients who failed to achieve complete ablation a reablation dose is recommended to have complete ablation outcome. Post second ablation dose some patients still have small residual thyroid tissue in the neck, that warrants small third ablation dose of ^{131}I to achieve complete ablation.
Aim
The aim of the current study is to compare ablation outcome post 30 mCi ablation dose of ^{131}I used as a second and as a third ablation dose.
Patients and methods
Retrospective analysis of data of 372 patients with papillary thyroid cancer confined to the thyroid gland referred post total thyroidectomy for ^{131}I ablation was performed. All received first ablation dose of 100 mCi of ^{131}I. Presence of residual thyroid tissue in follow-up ^{131}I whole body scan (WBS) with elevated unsuppressed serum thryoglobulin (Tg) level indicate incomplete ablation outcome. Those patients received 30 mCi of ^{131}I reablation on outpatient basis. Patients post second ablation dose with small residual thyroid tissue in the neck seen in follow-up ^{131}I WBS 6–9 months post second ablation dose with elevated serum Tg level received a third ablation dose of 30 mCi. Follow-up WBS and Tg level were performed 6–9 months post third dose to assess ablation outcome.
Results
Complete ablation rate post first dose was reported in 249 patients (66.9%). Out of the remaining 123 patients complete ablation was achieved post 30 mCi second ablation dose in 89 patients (72.4%) with an overall complete ablation post two doses achieved in 338 patients (90.9%). A third ablation dose of 30 mCi was given to the remaining 34 patients. Complete ablation was reported in 26 patients (76.5%), with statistically insignificant difference ($P>0.05$) between complete ablation outcome using 30 mCi as a second or as a third ablation dose. Successful complete ablation post three doses of ^{131}I (total dose of 160 mCi) was achieved in 364 patients (97.8%).
Conclusion
Complete ablation outcome rate between second and third ablation doses of 30 mCi of ^{131}I are comparable with no statistically significant difference.

DOI: 10.1530/endoabs.37.EP837

EP838

Well-differentiated thyroid cancer: the Philippine General Hospital experience

Tom Edward Lo, Abigail Uy & Patricia Deanna Maningat
Philippine General Hospital, Manila, Philippines.

Well-differentiated thyroid carcinoma (WDTC) is the most common thyroid malignancy. Although, associated with good prognosis, it may have a highly recurrent and fatal outcome in selected groups of patients. Filipinos in particular were reported to be the ethnic group with the highest incidence of thyroid cancer in several studies. Thyroid cancer among Filipinos were also observed to be more aggressive and recurrent in nature. This paper aims to describe the experience of a Philippine Tertiary Care Centre in managing patients with differentiated thyroid cancer. This is a retrospective cohort study of 723 patients diagnosed with WDTC (649 papillary and 79 follicular). We evaluated clinic–pathologic profile, ultrasound features, management received, clinical course, tumour recurrence, and eventual outcome during a mean follow-up period of 5 years. Mean age at presentation was 43 ± 13 for papillary thyroid cancer (PTC) and 44 ± 13 for follicular thyroid cancer (FTC). Majority of both PTC (63.2%) and FTC (54.4%) presented initially as stage 1. Greater FTC cases (12.7% vs 3.7%) presented with distant metastases with lung and bone being the most common. Nodal metastases at presentation were frequent among PTC (29.9% vs 7.6%). Majority of cases received complete thyroidectomy, subsequent radioactive iodine therapy and TSH suppression therapy which led to disease free state. Excluding patients with distant metastases at presentation, recurrence rates for papillary and follicular thyroid cancer were 30.1 and 18.8% respectively. Recurrences for PTC and FTC frequently occurred within 15–16 months from the initial post-surgical radioactive iodine therapy. PTC among Filipinos presents at a younger age, larger tumour size, higher distant metastases at presentation and a higher recurrence rate suggesting a more aggressive and recurrent behaviour for this type of thyroid malignancy. FTC among Filipinos also presents at a younger age and a higher recurrence rate but appears to behave similarly with other racial groups.

DOI: 10.1530/endoabs.37.EP838

EP839

Risk factors for recurrence in Filipinos with well-differentiated thyroid cancer

Tom Edward Lo, Abigail Uy & Patricia Deanna Maningat
Philippine General Hospital, Manila, The Philippines.

The incidence of recurrent well-differentiated thyroid cancer (WDTC) continues to rise as better imaging test and more sensitive monitoring improves disease surveillance. Despite its excellent prognosis, increasing morbidity from recurrent diseases continues to affect long-term outcome of most patients leading to higher medical cost and poorer quality of life. Filipino ethnicity in particular was reported to have the highest incidence of thyroid cancer with a highly aggressive and recurrent nature. This paper aims to identify associated risk factors for recurrence among Filipinos with WDTC. This is a retrospective cohort study of 723 patients diagnosed with WDTC seen at Philippine General Hospital (PGH). Study population was divided into groups based on presence or absence of recurrence. Recurrence was considered if the patient had clinical, biochemical or radiologic evidence of cancer remnants after surgery. Multivariable logistic regression analyses were used to determine significant predictors of recurrence. 214 (32.9%) patients with papillary thyroid cancer (PTC) and 23 (29.1%) patients with follicular thyroid cancer (FTC) developed recurrence within a median interval of 13 months and 26 months from thyroidectomy respectively. Age >45 (HR $=1.44$), multifocality of cancer (HR $=1.43$), nodal involvement (HR $=4.0$) and distant metastases at presentation (HR $=2.78$) were the risk factors identified to negatively impact the risk of recurrence for PTC. Follicular variant histology (HR $=0.60$)) and post-surgical radioactive iodine ablation therapy (HR $=0.31$) were protective factors for PTC recurrence. Distant metastases at presentation (HR $=19.4$) and post-surgical radioactive iodine ablation therapy (HR0.41) were identified for FTC recurrence. Lymph node metastases at presentation was the most important predictor of recurrence in PTC while it was distant metastases at presentation for FTC recurrence. Identified recurrence factors for WDTC among Filipinos in this study will be helpful in guiding the intensity of their treatment strategies and long-term thyroid cancer surveillance aimed to reduce future morbidity and mortality.

DOI: 10.1530/endoabs.37.EP839

EP840

Follicular variant of papillary thyroid carcinoma: an intermediate clinical entity

Tom Edward Lo, Abigail Uy & Patricia Deanna Maningat
Philippine General Hospital, Manila, The Philippines.

Follicular variant papillary thyroid cancer (FV-PTC) appeared to be the most common subtype representing between 9 and 22.5% of all PTC cases. With the dramatic increase in thyroid cancer incidence, FV-PTC has also been increasingly diagnosed in recent times. Despite its high incidence, the clinical behaviour, prognosis and outcome of FV-PTC remains controversial and challenging for most physicians. This study aims to compare the disease characteristics of FV-PTC with Classic-PTC and FTC in a single institution in the Philippines. This is a retrospective cohort study of 606 thyroid cancer patients diagnosed as C-PTC ($n=440$), FV-PTC ($n=87$) or FTC ($n=79$) by biopsy. Different clinical variables of three groups were then compared using a univariate logistic regression analysis. FV-PTC and C-PTC presented similarly with higher rates of multifocality (25.3% and 22.7% vs 7.6%) and bilateral involvement (20.7% and 17.1% vs 6.3%) as compared to FTC. C-PTC (37.7%) presented with high nodal involvement at presentation while both FV-PTC (8.1%) and FTC (7.6%) presented with less nodal metastases. Distant metastases was observed highest among the FTC (12.7%) group followed by FV-PTC (5.8%) and rarely in C-PTC (3.4%). Majority of patients underwent complete thyroidectomy and post-surgical radioactive iodine ablative therapy with similar rates across the groups. Recurrence rate was observed to be highest among C-PTC (39.4%) while FV-PTC (18.4%) had the lowest recurrence rate. FV-PTC resulted in almost 50% reduction (HR $=0.4934$; P value $=0.007$) in recurrence risk as compared with C-PTC. Mortality rate was highest among FTC (2.5%) group while FV-PTC (0%) and C-PTC (0.5%) had a similarly low mortality rate. FV-PTC represents a major sub-type of PTC that represents an intermediate entity between C-PTC and FTC. Although it behaves clinically like FTC presenting with lower lymph node metastases and higher distant metastases than C-PTC, its long-term survival and prognosis is quite similar with that of C-PTC. Treatment recommendations for C-PTC and FTC can be applied to FV-PTC cases.

DOI: 10.1530/endoabs.37.EP840

EP841

FNAC and frozen section correlation with definitive histology in thyroid diseases

Nithianantha Mayooran, Paeder Waters, Michael Kerin & Denis Quill
University Hospital Galway, Galway, Ireland.

Introduction
The ability to diagnose thyroid cancers pre-op or intra operatively by Fine needle aspiration cytology (FNAC) or frozen section (FS) leads to the delivery of appropriate one stage surgical management. We aim to study the concordance and discordance of FNAC and FS with final histology in thyroid pathologies.
Methods
All thyroid procedures from 2007 to 2011 ($n=423$), involving FNAC and or Frozen Section (FS) in their management pathway were included. FNAC ($n=159$) were classified in a five tier system (non-diagnostic, benign, atypical, suspicious or malignant). FS ($n=128$) were classified as inconclusive, benign, suspicious or malignant. FNAC and FS were correlated with final histopathology.
Results
Out of 159 FNAC 72 (40.8%, PPV 92.8%) showed correlation with final histology. 61 (38.3%) were reported undetermined as Atypical ($n=23$), follicular neoplasm ($n=27$) or suspicious for malignancy ($n=11$). Within 61 undetermined FNAC there were 25 malignancies (40.6%) detected in final histology. Frozen sections; 104 out of 128 showed correlation (81.2%, PPV 99.0%). 15 false negative and one false positive FS were noted. Out of six suspicious FS; four showed benign pathology and two showed malignancies. There were two inconclusive FS showed malignancies in histology.
Conclusion
In conclusion, until now FNAC is considered as the best modality to triage the thyroid nodule pre operatively. Atypical and follicular neoplasm cytology categories warrants further clinical assessment and close follow ups when appear benign. The intra operative frozen sections are helpful to perform a one stage operation for suspicious thyroid lesion. This study also highlights the recognised limitation of intra operative frozen section analysis of thyroid neoplasia.

DOI: 10.1530/endoabs.37.EP841

EP842

Clinical features, demographic, staging and prognostic factors in patients with microcarcinoma papillary thyroid

Rodriguez Ortega, Roldan Mayorga, Diaz Perez, Laínez López, Lopez Pérez & Rebollo Perez
Complejo Hospitalario Huelva, Hospital Juan Ramón Jiménez, Huelva, Spain.

Introduction
Papillary microcarcinomas tirodieos (MCT) are tumours less than or equal to centimeter size, mostly indectectables in the clinic and found incidentally after a thyroidectomy performed for another reason, management is under discussion and its prevalence is increased ~30%, it is believed that the increased use of thyroid ultrasound.
Review
16 patients with MCT in a province of southern Spain and evaluate the clinical and prognostic variables of our patients. Mostly women 15/1, age 44–74 years X 50. Most MCT found are incidental finding in Total thyroidectomy (TT) euthyroid BMN 13/16, other causes of surgery: Graves' disease 1/16 and 1/16 parathyroid adenoma. Hyperthyroidism 2/1. Histologically since, given the size average 4.4 mm, only one case of multifocality without capsular most or vascular invasion. In two cases has been extended thyroidectomy were no outbreaks of MCT. The capsular invasion and follicular variety associated with increased vigilance in our patients. They have only received 2/16 I131, the most aggressive. In terms of gender, our only case man is what has been presented with worse prognosis and clinical aggressiveness from the start. Our series is small, the follow-up time is short, but data obtained corroborate published prognostic factors, the most important gender, multifocality and lymphadenopathy. 2. The heterogeneity of this tumour requires us to individualise the approach, and close monitoring based on prognostic factors, to indicate the different strategies.

DOI: 10.1530/endoabs.37.EP842

EP843

Clinical significance of BRAF (V600E) mutation in papillary thyroid microcarcinoma

Jisun Park & Hye Kyung Shim
Inje University Haeundae Paik Hospital, Busan, Republic of Korea.

Objective
The purpose of this retrospective study was to correlate BRAF (V600E) mutation with clinicopathological characteristics in papillary thyroid microcarcinoma (PTMC).
Methods
We reviewed the clinical records of patients who were operated for a papillary thyroid microcarcinoma (PTMC) between May 2011 and October 2012 in Inje University Haeundae Paik Hospital. We investigated the prevalence of the BRAF (V600E) mutation, and relations between the presence of BRAF (V600E) mutation and clinicopathological characteristics (age, sex, tumour size, multiplicity, lymph node status and extrathyroid tissue invasion).
Results
Total 137 patients were included; 121 (88.3%) were female and 16 (11.7%) were male patients, aged from 22 to 74 years (mean age, 46.4 years). Median tumour size was 0.56 cm, ranging from 0.10 to 0.95 cm. The BRAF (V600E) mutation was identified in 82 patients (59.9%). Sixty patients (43.8%) had capsular invasion and 32 (23.4%) presented with some kind of extrathyroidal invasion of the tumour. Thirty-six patients had lymph node metastases; 32 (23.4%) to the central neck and 4 (2.9%) to the lateral neck. Three of four patients (75%) with lateral neck node metastases had BRAF (V600E) mutation, although this was not statistically significant. No statistically significant association was found between the BRAF (V600E) mutation and clinicopathological characteristics (age, sex, tumor size, multiplicity, lymph node status, capsular invasion and extrathyroid tissue invasion) of PTMC.
Conclusion
There was no significant association between the BRAF (V600E) mutation and any of the clinicopathological characteristics. However, we have noted that the prevalence of lateral neck node metastases was more frequent in patients with BRAF (V600E) mutation than those with WT BRAF, but this trend was not statistically significant.

DOI: 10.1530/endoabs.37.EP843

EP844

Follicular and papillary carcinoma in a subject with Graves' disease having aggravated orbitopathy following remnant ablation

Umut Mousa[1], Hasan Sav[1], Osman Koseoglulari[1] & Sebnem Aydin[2]
[1]Department Of Endocrinology and Metabolism, B Nalbantoglu Hospital, Nicosia, Cyprus; [2]Department of Nuclear Medicine, B Nalbantoglu Hospital, Nicosia, Cyprus.

Introduction
The risk for thyroid malignancy is higher in subjects with Graves' disease particularly papillary thyroid cancer (PTC). However, coincidence of both PTC and follicular thyroid cancer (FTC) in these subjects is rare. In this case report we present a subject with Graves' disease with a pathological diagnosis of PTC and FTC having aggravated orbitopathy following remnant ablation.
Case report
A 53-year-old subject was referred to our Endocrinology outpatient clinic with symptoms of retro bulbar pain and having TSH levels <0.05 (0.25–5.0 μIU/l) and FT4 67.3 pmol/l (10.6–19.4). The TSH receptor antibody level was 44 U/l (>9 (+)). She was negative for thyroglobulin and thyroid peroxidase antibodies. The thyroid ultrasound was reported as being compatible with thyroiditis with no visible thyroid nodule. Methimazole was initiated. 2 months after initiation of the anti-thyroid drug her eye pain increased in intensity and periorbital edema occurred. Total thyroidectomy was decided as the treatment option and early postoperatively her eye symptoms resolved. The pathology report was surprising. It was compatible with a 3 cm follicular carcinoma and a 3 mm papillary carcinoma follicular variant in the left lobe together with lymphocytic thyroiditis despite the ultrasound revealing no visible nodule. She received 100 mCi radioactive iodine for remnant ablation and glucocorticoid prophylaxis therapy was initiated. The patient lost contact and did not comply with the glucocorticoid treatment. 3 months after the radioiodine the patient admitted with diplopia, bilateral exophthalmos, chemosis, periorbital edema, spontaneous retro bulbar pane and pain on down gaze. Orbita MRI revealed bilateral thickening in the superior and lateral rectus muscles. She recently received pulse glucocorticoids therapy (7 gm in 10 weeks) and will receive orbital radiotherapy.
Discussion
Although occult microPTC is frequently observed in the thyroidectomy material of subjects with Graves' disease, it was surprising to visualize a 3 cm tumor pathologically but not radiologically. This could be explained by the very heterogeneous parenchyma masking the tumor. Aggravation of orbitopathy can be observed following remnant ablation for thyroid cancer in these subjects and glucocorticoid prophylaxis should be considered.

DOI: 10.1530/endoabs.37.EP844

EP845

Malignancy risk of thyroid nodules with repeated 'atypia of undetermined significance/follicular lesion of undetermined significance' diagnosis

Berrin Cetinarslan[1], Alev Selek[1], Emine Kivrakoglu[2], Zeynep Canturk[1], Ilhan Tarkun[1], Duygu Temiz[2] & Zeynep Akyay[1]
[1]Department of Endocrinology, Kocaeli University, kocaeli, Turkey; [2]Department of Internal Medicine, Kocaeli University, kocaeli, Turkey.

Introduction
'Atypia of undetermined significance/follicular lesion of undetermined significance' (AUS/FLUS) is a heterogeneous diagnostic thyroid fine needle aspiration biopsy (FNAB) category. AUS/FLUS is comprised of cases that cannot be definitively diagnosed as benign, suspicious for/consistent with neoplasm, suspicious for malignancy or malignant. The recommended management strategy for these cases is to perform a repeat FNAB after an appropriate time course. Although the estimated risk of malignancy for AUS/FLUS is reported 5–15%, there is growing evidence in the literature that suggest higher incidence of malignancy for this category The purpose of this study is to estimate the malignancy risk of repeated AUS/FLUS diagnosis of thyroid fine needle aspiration biopsies.
Methods
We report retrospective analyses of 56 cases with repeated AUS/FLUS diagnosis among 5396 thyroid FNABs. The demographic data and histologic follow-up were evaluated in the study. Histological outcome was categorised as benign, malignant or well-differentiated tumors of uncertain malignant potential (WDT-UMP).
Results
Initial AUS/FLUS diagnosis was 5.2% of our FNAB series. Among these 63 (22%) of were diagnosed again as AUS/FLUS on repeated FNAB. Seven patients were lost during follow-up. Among 56 cases with a repeated diagnosis of

AUS/FLUS, histologic follow-up revealed 28 (50%) benign outcome, 23 (41%) malignant outcome and 5 (9%) WDT-UMP outcome. The mean age was similar in both malignant and benign groups.
Discussion
The malignancy risk of AUS/FLUS category in thyroid FNABs was higher than anticipated in Bethesda System. The malignancy risk was reported up to 43% even with single biopsy in some studies. In current study the risk was 41% in repeated AUS/FLUS diagnosis. The reported malignancy rate of follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN) was 15–30%, for whom surgery is recommended management. Therefore, the management strategy of AUS/FLUS should also be revised as the malignancy rate was same or even higher than FN/SFN.

DOI: 10.1530/endoabs.37.EP845

EP846

Association of calcium-stimulated calcitonin values with pathological findings following total thyroidectomy

Georgios Papadakis, Ioannis Keramidas, Eleni Triantafillou, Foteini Kanouta, Theodora Pappa, Victoria Kaltzidou, Athanasia Tertipi, Gino Vecchini, Despoina Papadouli & Anastasios Pappas
Metaxa Cancer Hospital, Piraeus, Greece, Greece.

Background and objectives
Medullary thyroid carcinoma (MTC) originates from thyroid C-cells and is a calcitonin (CT) secreting tumour with aggressive behaviour. Surgery is recommended in all patients with basal or calcium-stimulated CT values of 100 pg/ml or higher due to the high probability of MTC. The objective of this study was to investigate the utility of calcium stimulation test for CT in order to distinguish MTC from C-cell Hyperplasia (CCH) preoperatively and to examine the histological findings of thyroidectomy in patients with peak stimulated CT >100 pg/ml.
Patients and methods
A total of 52 patients with thyroid nodules and basal CT levels between 6 and 100 ng/l had a positive calcium stimulation test (peak CT >100 ng/l) and underwent total thyroidectomy.
Results
patients (35%) were diagnosed with MTC and 34 (65%) with CCH. 20 patients (38%) had a differentiated carcinoma of follicular origin (DTCf) coexistent with either MTC or CCH. Calcium-stimulated calcitonin levels >452 ng/l had the optimal sensitivity and positive predictive value for differentiating MTC from CCH.
Conclusion
A large percentage of MTC may be identified by peak stimulated CT levels >100 pg/ml preoperatively, but overlapping calcitonin levels between MTC and CCH reduce the accuracy of the test. Remarkably, many patients with peak stimulated CT levels >100 pg/ml harbour a DTCf. A probable association between C-cell disease and DTCf needs further examination.

DOI: 10.1530/endoabs.37.EP846

EP847

Primary thyroid lymphoma: a heterogeneous disease and presentation of two different cases

Eleni Triantafillou, Georgios Papadakis, Ioannis Keramidas, Konstantinos Moustakas, Georgios Tsakonas, Paraskevi Manitarou, Aspasia Drosou, Olympia Tzaida, Athanasia Tertipi, Ioannis Tzaves, Aikaterini Megalakaki & Anastasios Pappas
Metaxa Cancer Hospital, Piraeus, Athens, Greece.

Background
Primary thyroid lymphoma (PTL) is a rare thyroid malignancy. Nevertheless, it frequently presents diagnostic and therapeutic challenges. We describe two patients with PTL with different clinical presentation/clinical picture and outcome.
Patients and methods
Two female patients underwent total thyroidectomy, the first, a 67-year-old female patient, because of nodular goitre and the second, a 79-year-old female patient, because of a large, painless thyroid mass accompanied by severe obstructive symptoms of the upper respiratory and gastrointestinal track.
Results
Histology of the first patient revealed lymphocytic thyroiditis and a small focus of previously unsuspected PTL, coexistent with an occult papillary thyroid carcinoma (PTC). The PTL was an incidental finding and 2 years after thyroidectomy she is free of disease without any further treatment. Histology of the second patient confirmed the clinical suspicion of PTL and established the diagnosis of a diffuse large B-cell lymphoma. Although she underwent standard chemotherapy, she died four months later.
Conclusions
PTL may have an aggressive and lethal course on the one end of the spectrum and the other one may be quite indolent. Our two cases confirm the heterogeneous nature of PTL.

DOI: 10.1530/endoabs.37.EP847

EP848

False-positive uptake of radioiodine WBS in a patient with papillary thyroid cancer due to a vertebral hemangioma

Eleni Triantafillou, Foteini Kanouta, Georgios Papadakis, Ioannis Tzaves, Evgenia Panagiotidi, Erasmia Trivizaki, Victoria Kaltzidou, Athanasia Tertipi, Aspasia Drosou & Anastasios Pappas
Metaxa Cancer Hospital, Piraeus, Athens, Greece.

Introduction
Diagnostic and post-therapy radioiodine whole body scan (WBS) is used in the follow-up of differentiated thyroid carcinoma (DTC) for the detection of local recurrence or remote metastasis. We report a case of false-positive uptake of radioiodine WBS.
Case report
A 37-year-old female patient underwent subtotal thyroidectomy for multinodular goitre and histology revealed multifocal papillary thyroid carcinoma, of follicular type with three foci of major diameter 1.35 mm. Post-operative radioiodine uptake of 24 h was 2.7% and thyroglobulin (Tg) levels were 35 ng/ml. Neck ultrasound was negative for pathologic lymph nodes and chest X-ray was unremarkable. An ablation dose of 70 mCi radioiodine was administered and the post-therapy WBS demonstrated multiple thyroid remnants on the anterior cervical region, increased uptake on the anterior upper mediastinum and a third large focus in the middle of the chest most evident on the posterior views suggesting vertebral metastatic involvement. Chest CT scan, cervical and mediastinal MRI were negative. In the 99Tc-bone scan a small focus of increased uptake was observed at the 8^{th} thoracic vertebrae with no other pathologic findings of the skeleton. MRI of the spine showed a high intensity pathologic signal in the 8^{th} thoracic vertebrae with a major frontal diameter of 14.6 mm, which is most likely attributed to an atypical hemangioma and not to metastatic disease, in line with the rather mild elevation of Tg levels. Bone metastases in DTC are known to cause higher Tg concentrations, usually >100 ng/ml.
Discussion
Vertebral hemangiomas are common and radioiodine uptake by a vertebral hemangioma in a patient with DTC has been reported in the literature in very few cases. These false positive results may mislead the physician to the presence of distant metastasis and erroneously change the stage of the disease and the therapeutic approach.

DOI: 10.1530/endoabs.37.EP848

EP849

Recurrent bone metastasis of follicular thyroid carcinoma with unknown primary site

Ji Oh Mok[1], Chong Hwa Kim[2], Sung Rae Kim[3], Seung Hee Yu[4] & Kiyoung Lee[4]
[1]Soonchunhyang University Bucheon Hospital, Bucheon, Republic of Korea; [2]Sejong General Hospital, Bucheon, Republic of Korea; [3]The Catholic University of Korea Bucheon ST.Mary's Hospital, Bucheon, Republic of Korea; [4]Gachon University Gil Hospital, Incheon, Republic of Korea.

Introduction
Occurrence of follicular thyroid carcinoma (FTC) is limited almost within thyroid gland, but distant metastasis is discovered uncommonly as first presentation. We experienced a rare case about recurrent bone metastasis of FTC with unknown primary site.
Case report
A 58-year-old woman complained about back pain for 3 years. A 5 cm sized mass in right 8th posterior rib was discovered and performed resection. The result of pathology was bone metastasis of FTC. Thirty four years ago, she underwent right thyroidectomy because of benign nodule. Thyroid USG shows no specific findings on remained left lobe of thyroid gland, but PET-CT presents increased uptake in the left thyroid gland, bilateral hilar and mediastinal regions, and right 8th rib. Left thyroid gland was removed totally, but primary FTC wasn't discovered in left lobe. After operation, she received radioactive iodine (RAI) ablation with 100 mCi. However, recurrent bone metastasis of right 8th posterior rib was found in PET-CT at 6 months after surgery. Repeated operation was performed for the lesion of right rib and pathological finding shows the same results as the first operation. Because of repeated bone metastasis and increased Tg level, she was ablated four times totally with 550 mCi and underwent recurrent operations for bone metastasis of right rib. One year later, metastasis of left temporal bone was found newly and removed surgically with cranioplasty. The result of pathology was a metastasis of FTC such as the previous result. Currently, the patient is followed up in the outpatient department for conservative treatment.
Conclusions
With unknown primary site, recurrent bone metastasis of FTC is a rare case and should be treated with appropriate therapy because of poor prognosis. We report a case about recurrent bone metastasis of FTC managed with repeated operation and RAI ablation.

DOI: 10.1530/endoabs.37.EP849

EP850

BRAF V600E positive papillary thyroid carcinoma is associated with suspicious ultrasound features

Julia Sastre-Marcos[1], Florentino Del Val-Zaballos[1], Claudia Cortes-Muñoz[1], Yolanda Campos-Martin[1], Sonsoles Aso-Manso[1], Ignacio Jaen-Diaz[2], Almudena Vicente-Delgado[1] & Jose Lopez-Lopez[1]
[1]Complejo Hospitalario de Toledo, Toledo, Spain; [2]Centro de Salud de Buenavista, Toledo, Spain.

Aims
To study if BRAF V600E mutation in thyroid fine needle aspiration (FNA) is associated with specific ultrasound (US) characteristics.
Patients and methods
From 2010 to 2014 we reviewed patients with thyroid nodules with the following inclusion criteria: US guided FNA of the nodule and molecular testing for BRAF V600E on the FNA. BRAF mutation was detected using fluorescence melting curve. An expert on US, blinded to the BRAF status reviewed US examinations and recorded the sonographic characteristics for each nodule. Six US characteristics were collected: margins, echogenicity, halo, nodular vascularization, calcifications and cystic or solid composition. US findings were classified into three categories: probably benign, indeterminate o suspicious. Demographic and clinical characteristics were also analysed. Univariate (χ^2 and student's *t*-test) and multivariate analysis were carried out.
Results
patients were studied (85, 6% women), mean age 52 years. 79 patients showed BRAF V600E mutations on FNA (29, 2%). BRAF-positive patients were younger (48.5 ± 16.0 vs 53.6 ± 16.1 years, $P < 0{,}05$) and with different gender distribution (men 21.5% vs 11.5%, $P < 0.05$). BRAF-positive nodules showed at least one malignant US characteristics in 89.9% vs 49.5% in BRAF-wild type nodules ($P < 0.001$). BRAF-positive nodules were classified as suspicious in 63.3% and as probably benign in 10.1%. BRAF-negative nodules were classified as suspicious in 24% and probably benign in 50, 5% ($P < 0.001$). By multivariate analysis, micro-macrocalcifications (OR 3.8 CI95% 1.8–8.0, $P < 0.001$) and hypoechogenicity (OR 2.7 CI95% 1.2–6.2, $P < 0.05$) were independently associated with the presence of BRAF V600E mutation.
Conclusion
Suspicious US characteristics are highly associated with BRAF positive FNA. Routine cervical US and molecular testing can contribute to improve preoperative risk classification of papillary thyroid cancer.

DOI: 10.1530/endoabs.37.EP850

EP851

Mixed medullary and papillary thyroid carcinoma – a case report

Emel Senol[1], Peyker Temiz[2], Yamaç Erhan[3] & Zeliha Hekimsoy[1]
[1]Medical Faculty, Department of Internal Medicine, Division of Endocrinology and Metabolism, Celal Bayar University, Manisa, Turkey; [2]Medical Faculty, Department of Pathology, Celal Bayar University, Manisa, Turkey; [3]Medical Faculty, Department of General Surgery, Celal Bayar University, Manisa, Turkey.

Thyroid cancers are divided into two main subgroups according to their embryonic origin: papillary cancer, the most common histologic type, seen in 75–80%, and medullary cancer, seen in 5–10% (sporadic or as a component of multiple endocrine syndrome). Because of the different phenotypic characteristics of these two cancers, it's unusual for them to present simultaneously. Since 1980, only a few cases of simultaneous papillary and medullary thyroid cancer have been reported. Medullary thyroid cancer may have follicular or papillary components, but it's very rare to see mixed medullary and papillary thyroid cancer in a single nodule (< 2 cm). In this article, we review the characteristics of one of our patients with mixed medullary and papillary thyroid cancer. A 59-year-old woman with a history of autoimmune hepatitis and primary biliary cirrhosis, was evaluated for a 16$\times$ 12 mm thyroid nodule in her right lobe. Finding medullary carcinoma by fine needle biopsy, she underwent total thyroidectomy with central lymph node dissection. Histopathologic examination of the tissues revealed 'thyroid medullary carcinoma fields meshed with papillary carcinoma sections'. Both medullary and papillary carcinoma components were confirmed immunohistochemically. The main component of the mixed tumour was medullary carcinoma. The patient will be followed up in our Endocrinology and Metabolism Clinic. The incidence, histopathological structures, treatment, and follow up of papillary and medullary thyroid carcinomas are different. The presence of medullary thyroid carcinoma mandates further investigation to see whether other components of MEN syndromes are present, and to evaluate other family members for similar problems. The prognosis of papillary carcinoma is better than medullary thyroid cancer. The recurrence and mortality rates of medullary cancer are higher, in direct proportion to the size of the primary lesion. Mixed thyroid carcinomas are rare and are difficult to diagnose preoperatively by fine needle biopsy alone.

DOI: 10.1530/endoabs.37.EP851

EP852

Testosterone and pituitary hormones levels in thyroid cancer males patients

Eugen Luchytskiy, Vitaliy Luchytskiy, Galina Zubkova, Victoriya Rybalchenko, Valentyn Markov & Sergiy Gulevatyy
SE 'Institute of endocrinology and metabolism named after V.P. Komissarenko National Academy of Medical Science of Ukraine', Kyiv, Ukraine.

The high pprevalence of thyroid cancer among the male population of Ukraine during the active reproductive age (over 25 years) makes it reasonable to study the effect of the disease on testicular function. The purpose of work was to examine the state of androgen levels and pituitary hormones in men with thyroid cancer.
Design and methods
The study involved 14 male patients aged from 21 to 40 years, with thyroid cancer. The control group were 46 healthy men aged from 20 to 45 years. All patients underwent determination of serum levels of total testosterone (tT), luteinising hormone (LH), *follicle-stimulating hormone* (FSH) and prolactin before surgery and one month after.
Results
The study of pituitary hormones and testosterone in surveyed patients showed that the average concentration of pituitary hormones in male patients with thyroid cancer before and after surgical treatment was not significantly different from that of the control group and were within the normal vibrations. Average levels of LH were 5.7 ± 1.2 IU/l before surgery and 6.0 ± 1.1 IU/l after ($P > 0.5$), and do not differ from control group (4.6 ± 0.4 IU/l). Average FSH levels were 6.5 ± 1.1 IU/l before surgery vs 5.5 ± 1.8 IU/l ($P > 0.5$), as well 5.3 ± 0.5 IU/l in controls. The average levels of tT in men with thyroid cancer had trend to decrease after thyroidectomy from (16.4 ± 0.5) nmol/l to (15.6 ± 0.4) nmol/l ($P = 0.05 < 0.1$). However, these parameters were within normal fluctuations euhonadal men and did not differ significantly from that of the control group (19.1 ± 1.7) nmol/l.
Conclusion
These data confirm that short-term failure of the thyroid gland is not pronounced adverse effect on testicular testosterone production.

DOI: 10.1530/endoabs.37.EP852

EP853

Detection of somatic oncogene alterations in FNA samples of cold nodules and 3 years follow-up of patients in Hungary

Bálint Tobiás[1,3], Bernadett Balla[1,3], P János Kósa[1,3], István Takács[1], Zsolt Nagy[1], Péter Horváth[1], Balázs Járay[2], Eszter Székely[2], Roland Istók[2], Tamás Székely[2] & Péter Lakatos[1]
[1]1st Department of Internal Medicine, Semmelweis University, Budapest, Hungary; [2]2nd Department of Pathology, Semmelweis University, Budapest, Hungary; [3]Pentacore Laboratory, Budapest, Hungary.

Cold nodules are one of the most common findings on scintigraphic examinations of the thyroid gland. About 5–10% of these nodules turn out to be histologically malignant. Our aim was to examine some somatogenetic alterations associated with thyroid cancer in FNA samples of the thyroid. These alterations included single nucleotide mutations (BRAF, HRAS, NRAS, KRAS) and genetic translocations (RET/PTC1, RET/PTC3, PAX8ex7/PPARgamma, PAX8ex9/PPARgamma). The SNPs were tested by real-time PCR with fluorescence melting curve analysis and the rearrangements were detected by Taqman probe-based quantitative real-time PCR. We have analysed 779 consecutive FNA samples and followed up the patients 3 years long. In the examined 779 samples, we found different genetic alterations (39 BRAF, 23 NRAS, 9 HRAS, 1 KRAS mutations and 1 RET/PTC3 rearrangement). After 1 year follow-up by histology, 52 cases (6.8%) were classified as malignant, from which we identified genetic alterations only in 40 (5.1%). (specificity 93.3%, sensitivity 46.2%, negative predictive value 96.0%, positive predictive value 32.9%) In two years follow-up group ($n=504$) by histology, 30 cases (6.0%) were classified as malignant, from which we identified genetic alterations in 26 (5.2%). In three years follow-up group ($n=250$) by histology, 13 cases (5.2%) were classified as malignant, from which we found genetic alterations in 14 (5.6%). No PAX8/PPARgamma rearrangements were demonstrated in the 779 samples. These data are not in complete accordance with published information. This fact might be due to several factors including the differences in iodine supply in different geographical areas.

DOI: 10.1530/endoabs.37.EP853

EP854

Primary thyroid lymphoma: an ominous and commonly forgotten association with Hashimoto's thyroiditis

Cherng Jye Seow[1], Davin Ryanputra[2], Tian Ray Lai[1], Chin Ee Ong[1], Minyang Chow[1], Grace Lum[1], Claire Min-Li Teo[1] & Zhiguang Ng[1]
[1]Tan Tock Seng Hospital, Singapore, Singapore; [2]Yong Loo Lin School of Medicine, Singapore, Singapore.

Introduction
Primary thyroid lymphoma (PTL) is rare and constitutes 2–5% of thyroid malignancies. The risk however increases with background Hashimoto's thyroiditis. (HT) We report a patient with HT complicated by thyroid lymphoma and did a literature review on this topic.
Case presentation
A 61-years-old Chinese lady with background HT on levothyroxine presented with an enlarging goitre of 6 months duration. There was weight loss of 3–4 kg, but no fever or night sweats. Examination showed an enlarged, non-tender thyroid gland with no palpable cervical lymph node. US showed a lobulated heterogeneous mass measuring $5.5\times3.2\times2.9$ cm with internal vascularity. FNAC was suspicious for a lymphoma. CT neck, thorax and abdomen showed a $6.7\times7.0\times4.1$ cm mass with possible infiltration through the left lateral tracheal wall and encasement of the left common carotid artery. There was no significant lymphadenopathy. Referral to the oncologist was made.
Discussion
PTL has an estimated annual incidence of two cases per million and almost all are of B-cell origin. It affects middle-aged to older individuals, predominantly women. Most are diagnosed with stage I disease and the most common histologic subtype is diffuse large B-cell lymphoma. The likelihood of developing thyroidal lymphoma is 40–80 times greater in patients with chronic thyroiditis. Proposed mechanisms include prolonged antigenic stimulation in the setting of autoimmune thyroiditis leading to lymphomatous transformation or malfunction of the somatic hypermutation process, a phenomenon called aberrant somatic hypermutation process, which is regarded as a mechanism of lymphomagenesis. Treatment comprises different modalities depending on histologic subtype and stage of disease.
Conclusion
The diagnosis of PTL should be considered in a rapidly growing goiter especially in the background of HT. Early detection may result in improved survival.

DOI: 10.1530/endoabs.37.EP854

EP855

Vitamin-D neutralising CYP24A1 gene expression in thyroid fine-needle aspiration biopsy samples

Bernadett Balla[1], Péter Horváth[1], Bálint Tobiás[1], Gabriella Győri[2], Balázs Járay[3], János Kósa[1,4] & Péter Lakatos[1,4]
[1]PentaCore Laboratory, Semmelweis University, Budapest, Hungary; [2]Department of Radiology and Oncotherapy, Semmelweis University, Budapest, Hungary; [3]2nd Department of Pathology, Semmelweis University, Budapest, Hungary; [4]1st Department of Internal Medicine, Semmelweis University, Budapest, Hungary.

Objectives
We previously published the result of CYP24A1 gene expression in one hundred, solely papillary thyroid carcinoma (PTC) compared to its own tumour free control from the same patient. We report an increase in CYP24A1 gene transcription in more than half of analysed PTCs. Elevated CYP24A1 protein expression was also observed in the cancerous tissue section compared to peritumoural normal thyroid tissue. In the present study we aimed to examine CYP24A1 gene transcription in thyroid fine-needle aspiration biopsy (FNAB) specimens and follow up the patients for 2 years.
Methods
The gene expression analyses of 42 thyroid FNABs were carried out by Taqman probe-based quantitative real-time RT-PCR. The somatic mutation states of BRAF, NRAS, HRAS, KRAS oncogenes as well as ELE1/RET and CCDC6/RET rearrangements were also tested. Genomic DNA and total RNA were isolated from each sample using Roche High Pure kits.
Results
Eight males and 34 females participated in the study. The mean age was 51.43 years. Cytology results of 28 FNABs were benign and 14 were malignant. Within the malignant specimens 13 papillary and 1 follicular type carcinoma were recognised. Altogether, 6 BRAF (rs113488022) mutations, 1 ELE1/RET translocation were detected in the malignant FNAB samples and one benign biopsy carried HRAS (rs28933406) mutation. CYP24A1 gene expressions were noticed only in five FNAB samples diagnosed with PTC. We could not determine CYP24A1 specific mRNA in the benign samples. During the follow up period we identified malignant transformation in three cases from the 28 initially cytological benign FNABs. In all of these three cases PTC were certified.
Conclusion
It is well established, that CYP24A1 gene activity is elevated in various cancers including thyroid carcinoma might be to protect tumour tissue from the anti-proliferative and pro-apoptotic effects of 1.25-vitamin D3. Our results show that changes of CYP24A1 gene expression have no predictive value in precancerous states of thyroid and it could not help to complete the diagnosis of FNAB cytology.

DOI: 10.1530/endoabs.37.EP855

EP856

Brain metastases of thyroid carcinoma: a report of two cases and review of the literature

Ahmed-Ali Leila, Fedala Nora Soumeya & Chentli Farida
Department of Endocrinology, Metabolic Disease Bab El Oued Hospital, Algiers, Algeria.

Introduction
Brain metastases of thyroid carcinomas are rare (0.1–5%) according to the literature data. They generally occur in a context of metastatic spread which has a serious impact on survival. We report two cases and will review the literature data.
Observations
Case 1: 57-year-old patient monitoring for papillary thyroid carcinoma in its solid form trabecular classified T4N0M1with lung metastases. Following a neurological symptoms of tonic-clonic type of the left arm cerebro-spinal MRI revealed a 20 mm right parietal lesion and cerebellar lesion 4 mm. The rest of the staging finds multiple hepatic nodules probably metastatic. Up-take scan after radioiodine therapy was positive in cervical, brain and lung. thyroglobulin rates are increased to 3050 ng/ml.
Case 2: 11-year-old patient with a vesicular thyroid carcinoma with multiple secondary metastases: brain, lung, bone, pancreas, liver. The histological study of parietal localization confirmed his thyroid origin. Up-take scan after radioiodine therapy was positive especially in brain. thyroglobulin levels are increased to 8000 ng/ml.
Conclusion
Patients with thyroid carcinoma metastatic to the brain appear to have a relatively short survival time compared with other patients with thyroid carcinoma,

although this survival time is significantly longer than that noted with other solid tumour metastases to the brain. Early detection is important and specific treatment (radioiodine therapy) and standard treatments (surgery, Whole Brain Radiation Therapy) can improve their prognosis.

DOI: 10.1530/endoabs.37.EP856

EP857

Aggressive papillary thyroid cancer with rare morphological features: a case report

Umut Mousa[1], Osman Koseoglulari[1], Sebnem Aydin[3], Minel Ozen[2], Hasan Sav[1] & Varol Esatoglu[4]
[1]Department of Endocrinology and Metabolism, B Nalbantoglu Hospital, Nicosia, Cyprus; [2]Deparment of Pathology, B Nalbantoglu Hospital, Nicosia, Cyprus; [3]Deparment of Nuclear Medicine, B Nalbantoglu Hospital, Nicosia, Cyprus; [4]Department of General Surgery, B Nalbantoglu Hospital, Nicosia, Cyprus.

Introduction
Papillary thyroid cancer (PTC) is the most frequently observed type of thyroid cancer. It usually shows favorable prognosis although some aggressive pathological subtypes have been defined. In this case report we present an aggressive form of PTC with previously non defined histological features.
Case report
At initial evaluation the subject presented with a mass in the neck. Neck ultrasonography (USG) revealed a 49×23 mm hypo echoic nodule in the left lobe and multiple lymphadenopathies adjacent to the left thyroid lobe being suspicious for malignancy. The nodule had irregular edges and was hyper vascular in power doppler imaging (PDI). The patient underwent total thyroidectomy and ipsilateral central lymph node dissection. The pathology report was compatible with papillary thyroid cancer (PTC) and Hashimoto's thyroiditis. The tumour was composed of 30–35% insular, 10% Tall-Cell and 55% anaplastic cells. The tumour was 45mm in size and showed pericapsular soft tissue invasion. Immunohistochemistry was positive for Thyroglobulin, TTF-1, NSE, Pan SK and CK 19. And negative for CEA, Calcitonin, chromogranine and synaptophysin. Ki 67 proliferation index was 5–6%. PET CT revealed multiple metastases in the liver, lungs, thoracic and lumbar vertebra. The patient is actively receiving chemotherapy at the Medical Oncology department in our hospital.
Result
Although PTC generally shows favourable prognosis the histomorphological features are variable and may not suit one of the previously defined PTC subtypes. Such cases as the one defined may clinically advance like anaplastic thyroid cancer.

DOI: 10.1530/endoabs.37.EP857

EP858

The evaluation of sex hormone receptors in papillary thyroid cancer as an additional tool in the post-operative risk stratification and in the pre-gravidic counselling of women with persistent disease

Laura Fugazzola[1,5], Simone De Leo[1,2], Michela Perrino[1,2], Stefania Rossi[3], Delfina Tosi[4], Valentina Cirello[5], Carla Colombo[1,2], Gaetano Bulfamante[3,4], Leonardo Vicentini[6] & Guia Vannucchi[1]
[1]Endocrine Unit, Fondazione IRCCS Ca' Granda, Milan, Italy; [2]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; [3]Division of Pathology, San Paolo Hospital, Milan, Italy; [4]Department of Health Sciences, University of Milan, Milan, Italy; [5]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; [6]Endocrine Surgery Unit, Fondazione IRCCS Ca' Granda, Milan, Italy.

Thyroid cancer is highly prevalent in women aged 15–44 years, suggesting that in females the fertile age could be regarded as a risk factor. Consistently, in the last decades epidemiological and experimental findings indicated a possible role of oestrogens in the development and progression of differentiated thyroid tumours. We studied the expression of oestrogen receptor α (ER α) and Progesteron receptor (PR) in 182 female and male patients with papillary thyroid cancer (PTC) and correlated it to clinical and molecular features. ER α and PR expression was found in 66.5 and 75.8% of patients respectively, and significantly correlated with larger tumour size and with the presence of metastatic neck lymph-nodes at diagnosis. Interestingly, the occurrence of the 'receptor conversion' phenomenon, already reported to have a negative prognostic effect in breast cancer, has been demonstrated for the first time in thyroid tumours. Indeed, almost all the ER α positive primary tumours analysed had ER α negative metastatic lymph-nodes. $BRAF^{V600E}$ mutation was detected in 23.2% of the tumours, with a higher prevalence in larger tumours and in those with a stronger ER α or PR staining. Finally, the follow-up of a woman with persistent PTC during pregnancy, highlighted the role of oestrogens in the progression of the disease. In conclusion, the expression of ER α and PR is frequent in PTC tumour tissues and it is significantly associated with a more aggressive presentation. Although their expression did not seem to influence the outcome of the disease, the evaluation of sex hormone receptors could be an additional tool in the post-operative risk stratification and might be useful in the pre-gravidic counselling of fertile women affected with persistent thyroid cancer.

DOI: 10.1530/endoabs.37.EP858

EP859

Concomitant papillary thyroid cancer and graves' disease: an ominous association

Davin Ryanputra[1] & Cherng Jye Seow[2]
[1]Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore; [2]Tan Tock Seng Hospital, Singapore, Singapore.

Background
Papillary thyroid carcinoma (PTC) in patients with background Graves' disease (GD) has been associated with a higher risk of post-operative tumour recurrence. We present a case and review the literature for possible explanations.
Case presentation
A 55-year-old gentleman with GD treated with carbimazole presented 1 year after initial diagnosis with a 3 cm palpable thyroid nodule. Fine needle aspiration cytology (FNAC) was suggestive for malignancy. A total thyroidectomy with prophylactic central-compartment neck dissection was done-stage 3 papillary thyroid cancer (T3N0M0); size of tumour: 4.7×2×2 cm. There was no lymphovascular invasion or features of aggressive histology. He received 150 millicurie of 131-radioactive iodine (RAI) and was started on high dose L-thyroxine, keeping thyroid stimulating hormone (TSH) suppressed. Thyroid-stimulating hormone receptor antibody (TRAb) levels was positive at 3.3 IU/L (NR: <1). 2 years post operatively, a follow-up neck ultrasound revealed prominent lymph nodes. FNAC was positive for malignancy. There were no distant metastases. He had neck dissection followed by RAI.
Discussion
Neoplastic cells of differentiated thyroid cancer, like normal thyroid cells, express functional receptors for TSH. Thyroid stimulating antibodies might play a role in stimulating thyroid cancer growth, invasiveness and angiogenesis by up-regulating vascular endothelial growth factor, placenta growth factor, and their receptors. The antibodies have also been shown to initiate cellular proliferation by suppressing mitochondrial reactive oxygen species levels, preventing apoptosis. Apart from that, different growth factors that probably are produced by the over-stimulated (by TRAb) and hypervascularised thyroid could also affect the growth and metastases of thyroid cancer in patients with GD. Interleukins four and ten, locally produced in thyroid glands affected by GD, also have a strong anti-apoptotic effect on malignant thyrocytes.
Conclusion
A high index of suspicion for tumour recurrence in patients with PTC and concomitant Graves' disease is necessary.

DOI: 10.1530/endoabs.37.EP859

EP860

Rise in incidence of differentiated thyroid cancer in the south of Spain

Florentino Carral[1], Gema Ruiz[2], Raquel Tinoco[2], Julio González-Outon[4], Vicente Vega[3], Maribel Robles[3], Ana Isabel Jiménez[1], Concepción García[1] & Carmen Ayala[1]
[1]Endocrinology Department, Puerto Real University Hospital, Puerto Real, Cádiz, Spain; [2]Internal Medicine Department, Puerto Real University Hospital, Puerto Real, Cádiz, Spain; [3]Surgery Department, Puerto Real University Hospital, Puerto Real, Cádiz, Spain; [4]Clinical Information Department, Puerto Real University Hospital, Puerto Real, Cádiz, Spain.

Background
Recent studies have shown that the incidence of differentiated thyroid cancer (DTC) is increasing.
Objective
Evaluate the incidence of DCT in a center of the south of Spain for the last 15 years and analyse the clinical and morphological factors related to DTC.

Methods
We reviewed the series of patients undergoing thyroid surgery at our hospital over a 15-year period and identified patients with DTC. Patients were divided in three periods: 2000–2004, 2005–2009 and 2010–2014 and incidence rates were calculated. The variables gathered were age, sex, date of diagnosis, clinical presentation, hormonal status and cytology, size, morphology and extension of the tumour.
Results
patients with DTC were diagnosed. A significant increase in the number of DTC was shown in the period ranging from 2010 to 2014 (105 cases; 17.1% of the surgeries) compared to 71 cases between 2005 and 2009 (14.2% of interventions) and 48 cases between 2000 and 2004 (9.8% of interventions) ($P<0.001$). Incidence rates also increased from 3.7 (2000–2004 period) to 4.8 (2005–2009 period) and 6.8/1 00 000 habitants (2010–2014 period) ($P<0.001$) and this trend was found in both genders. The incidence was 3.1 times higher in women than in men and the most frequent morphology was papillary carcinoma (90.6%). No differences were found in the prevalence of microcarcinoma, extrathyroidal extension, lymph node involvement or distance metastases in the analysed periods.
Conclusions
We report a similar rise in the incidence of DTC in the south of Spain to the overall reported in the international literature.

DOI: 10.1530/endoabs.37.EP860

EP861

Our experience in the treatment of Thyr3 and Thyr4 nodules

Elisa Bertocchi, Paolo Del Rio, Lorenzo Viani, Annarita Totaro & Mario Sianesi
General Surgery and Organ Transplantation, University Hospital of Parma, Parma, Italy.

Introduction
The Bethesda System 2010 introduced six diagnostic categories and divided follicular proliferation in two risk classes: Thyr3 and Thyr4. In literature about 5–15% of Thyr3 nodules are malignant and the risk of malignancy for Thyr4 is closer to 15–30%. We have analysed our cases surgically treated in recent years.
Materials and method
We have prospectively categorised into a dedicated database patients submitted to thyroidectomy at OU General Surgery and Organ Transplantation, University Hospital of Parma, from January 2012 to December 2014. The following data were recorded: age, sex, cytological category and histological examination.
Results
patients were submitted to total thyroidectomy for suspected or definite diagnosis of differentiated thyroid cancer (DTC). In 145 cases cytological categories were Thyr3 (48 patients: 43 females and five males; average age 50.3 years) and Thyr4 (97 patients: 79 females and 18 males; average age 49.7 years). In 16 patients with Thyr3 (33.3%)and in 40 patients with Thyr4 (42.85%) nodules were malignant.
Conclusion
In our area the percentage of thyroid nodules is high; the incidence of malignant nodule in females is closer to 18 cases/1 00 000 person-years. This element explains the higher incidence of malignancy of Thyr3 and Thyr4 nodules in our series compared to data in the literature.

DOI: 10.1530/endoabs.37.EP861

EP862

Anaplastic thyroid carcinoma: The failure of conventional therapy but the real promise of targeted therapy

Paul Lennon[1], Sandra Deady[2], Marie-Louise Healy[1], John Kinsella[1], Conrad Timon[1] & James Paul O'Neill[3]
[1]St. James's Hospital, Dublin, Ireland; [2]National Cancer Registry, Cork, Ireland; [3]Royal College of Surgeons, Ireland, Dublin, Ireland.

Introduction
Anaplastic thyroid cancer is a devastating disease with median survival between 1.2 and 10 months. The disease accounts for as little as 0.9–1.6% of total thyroid cancer cases, but may account for up to half of all thyroid cancer mortality. The aim of our study is to evaluate the prognostic factors and outcomes of patients diagnosed with anaplastic thyroid cancer in Ireland and review emerging treatments for this disease.
Methods and design
A retrospective analysis of the National Cancer Registry in Ireland was undertaken, for patients with a diagnosis of anaplastic thyroid cancer between 2000 and 2010. Patient, tumour, and treatment characteristics were recorded. The Kaplan–Meier method was used to determine overall survival and factors predictive of outcome were determined by univariate and multivariate analysis by cox regression using Stata 13 software.
Results
Of a total of 64 patients, 40 were female and 24 were male. The median age was 69, and 27.5% of patients had distant metastases at diagnosis. The overall median survival was 2.3 and the 6 months, 1, 2, and 5 year overall survival was 23.4, 12.5, 6.25, and 4.69% respectively. On univariate analysis age, gender, metastases at diagnosis, surgery, radiotherapy, and multimodality treatment were statistically significant indicators of prognosis, and metastases at diagnosis remained statistically significant on multivariate analysis. A review of the7741 patients in the literature revealed a median survival of 3.67 months.
Conclusions
The British and American Thyroid associations (BTA/ATA) have comprehensive guidelines on the management of ATC. However due to the rapidity of onset of the tumour, few patients benefit substantially from aggressive conventional treatments, and survival has not changed over a period of 40 years. Personalised therapeutic approaches based on the use of targeted therapy may be the best hope to improve treatments for patients with ATC.

DOI: 10.1530/endoabs.37.EP862

EP863

Polymorphisms of cdkn1b gene may influence hereditary medullary thyroid carcinoma aggressiveness

Raquel Bueno Barbieri[1], Lucas Leite Cunha[1], Natassia Elena Bufalo[1], Danilo Villagelin[1,3], Lígia Vera Assumpção[1], Rui Monteiro Maciel[2], Janete Maria Cerutti[2] & Laura Sterian Ward[1]
[1]University of Campinas – UNICAMP, Campinas/SP, Brazil; [2]Federal University of São Paulo – UNIFESP, Sao Paulo/SP, Brazil; [3]Pontificia Universidade Católica de Campinas – PUCC, Campinas/SP, Brazil.

Despite the importance of the Ret receptor, it is clear that other signal transduction pathways, tyrosine kinase receptors, and tumours suppressor genes are involved in MTC tumorigenesis and progression. Differences in the clinical behaviour of patients harbouring the same Ret mutations may be related to these other genes. Alterations of genes involved in the G1 phase of the cell cycle, including the cyclins, CDKs and CDK inhibitors, are common events in neoplastic development of a series of different types of tumours. The role of key cell cycle regulations genes in hereditary medullary thyroid cancer (HMTC) is still largely unknown. In order to evaluate the influence of inherited polymorphisms of CDKN1B (rs2066827, rs34330), CDKN2C (rs12885) and CDKN2A (rs11515) genes in the pathogenesis of HMTC, we used TaqMan SNP genotyping to examine 138 HMTC patients. All patients were previously genotyped for RET gene and mutations are: 81 in codon 533 3 in codon 618 1 in codon 609 51 in codon 634 and two patients in codon 804.
A multivariate logistic regression analysis demonstrated that CDKN1B (34330) gene polymorphism inheritance was related to HMTC aggressiveness. Wild type (CC) rs34330 CDKN1B patients presented larger tumours (1.4 ± 1.38 cm) than polymorphic (TT) patients (0.6 ± 0.65 cm; $P=0.044$). In the same way, wild type (CC – 29.3 ± 15.6 years) rs34330 CDKN1B gene patients are younger than heterozygous patients (CT – 42.1 ± 18.2 years; $P=0.029$). We were unable to find any other association between the profile of the CDKN1B (rs2066827), CDKN2C (rs12885) and CDKN2A (rs11515) genes and patients' clinical or pathological characteristics. This study is first to investigate the association of CDKN1B, CDKN2C and CDKN2A polymorphisms and the aggressiveness to HMTC and suggests that profiling cell cycle genes may help define the risk and characterize HMTC aggressiveness, hence identifying patients who could benefit of a closer follow-up.

DOI: 10.1530/endoabs.37.EP863

EP864

A cavernous angioma-mimicking case of solitary bone and brain metastasis of the columnar cell variant of papillary thyroid carcinoma

Mikyung Kim, Namkeong Kim, Yeyeon Lee, Nanhee Cho & Hyesoon Kim
Keimyung medical school, Daegu, Republic of Korea.

Background
Thyroid carcinoma has increased annually. Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy and thought to have favourable prognosis. Distant metastases are common in lungs and bones. However, brain metastases are rare and its prognosis is unfavourable. Here we reported a case of solitary brain metastases of PTC mimicking cavernous angioma in a 76-year-old woman patient.
Methods
We collected her data retrospectively.
Results
A 76-year-old woman presented memory disturbance for 3 months. On physical examination, there was a 5 cm sized mass without tenderness in sternum. The brain magnetic resonance image showed a lobulated lesion with a mixed signal core surrounded by low intensity rim in right frontal lobe that was not enhanced in contrast image suitable for a cavernous angioma with haemorrhage. There was a mass with necrosis in the manubrium on chest computed tomography (CT) but no abnormality in abdomen CT. We did craniotomy for tumour removal and manubrium mass biopsy in the same day. In pathological finding, brain and manubrium revealed metastatic carcinoma consistent with primary in thyroid. For investigation of thyroid cancer, we did a neck ultrasonography and it demonstrated 1 cm sized hypoechoic nodule with coarse calcification in the left isthmus. As a result of fine needle aspiration on left thyroid nodule, pathology showed a classic PTC and BRAF mutation was positive. The patient refused thyroidectomy and expired 9 months later due to pneumonia and sepsis.
Conclusion
Brain metastases with PTC mimicking cavernous angioma is extremely rare. It makes us cautious that even small PTC could occur as distant metastasis.

DOI: 10.1530/endoabs.37.EP864

EP865

Incidental papillary thyroid carcinoma prevalence in benign multinodular goitre: data from Northern Portugal

Maria Teresa Pereira, André Couto de Carvalho, Cláudia Freitas & Fátima Borges
Division of Endocrinology, Diabetes and Metabolism, Centro Hospitalar do Porto, Porto, Portugal.

Introduction
Incidental papillary thyroid carcinoma (PTC) in patients undergoing thyroidectomy for benign multinodular disease is a well-recognised finding. Its true prevalence remains uncertain and shows great variability between studies, ranging from 7–25%. Our purpose was to review the prevalence of PTC in thyroid glands removed for benign nodular disease at a Northern Portuguese tertiary hospital.
Methods
From December 2012 to December 2014, the histological reports of patients treated surgically for benign nodular thyroid disease were reviewed. We excluded patients with thyroid hyperfunction and those with any suspicious cytological findings (*Bethesda category* $\geq$III). Data regarding demographics and pathological findings were retrieved.
Results
patients were included in the analysis, with a mean age of 55 ± 15 years; 87% were females. The overall prevalence of malignancy (PTC) found was 15.8% (95% CI, 11.4–21.5%). There were no statistically differences between PTC and benign groups regarding patient's age and gender. The pathological tumour size ranged between 1 and 55 mm (median 8 mm). Most cases of PTC were microcarcinomas (19 in 32, 59.4%), with a median diameter of 4 mm (range, 1–9 mm). In respect to macrocarcinomas (13 in 32, 40.6%), the median tumour diameter was 35 mm (range, 11–55 mm). In seven patients (22%), the tumour was multifocal and in one patient (3%) vascular invasion was documented. The most common variants of PTC found were classical and follicular with 59.4 and 37.5% respectively.
Conclusions
In our series, microscopic PTC prevalence in patients undergoing thyroid surgery for benign euthyroid disease seems to be similar to the previously described. These high rates of pathological incidental thyroid carcinomas should be taken into account and drive appropriate diagnostic and therapeutic approaches.

DOI: 10.1530/endoabs.37.EP865

EP866

Serum Galectin-3 in papillary thyroid cancer: preliminary results

Andra Caragheorgheopol[1,2], Sorina Schipor[1,2], Dana Manda[1,2], Ana-Maria Stefanescu[1,2], Dumitru Ioachim[1,2] & Corin Badiu[1,2]
[1]National Institute of Endocrinology 'C. I. Parhon', Bucharest, Romania; [2]University of Medicine and Pharmacy 'Carol Davila', Bucharest, Romania.

Background
There are only few reports regarding the role of serum galectin-3 (Gal-3) as an early biochemical marker in thyroid carcinoma.
Aim
To evaluate the potential overexpression of Gal-3 in sera from patients with confirmed diagnosis of papillary thyroid carcinoma (PTC).
Patients and methods
We retrospectively investigated serum Gal-3 in 40 patients referred to the surgical department for thyroidectomy. Sera were collected before surgery. We measured sera of 40 patients (mean age 48.79 ± 14.15 years): 32 women (82.5%) and seven mens (17.5%). Patients were divided in four groups, based on histopathological stage: nodular goitre, PTC1, PTC2, PTC3/4. Gal-3 was measured by Elisa (Abcam, UK); sensitivity 0.12 ng/ml, intra-assay cv 6.4%, inter-assay cv 11.4%. The study was approved by Ethics Committee of the Institute.
Results
patients showed different PTC stages at histopathological exam, as follows: 10 PTC1, 10 PTC2 and 11 PTC3/4, respectively; nine patients were diagnosed with benign nodular goitre. We found a significant difference between cancer and non-cancer patients (median Gal-3 – 8.427 ng/ml vs 4.402 ng/ml, $P = 0.019$), between PTC3/4 patients and those with nodular goitre (median Gal-3 – 9.069 ng/ml vs 4.402 ng/ml, $P = 0.0097$), and between PTC1 and goitre patients (median Gal-3 – 8.751 ng/ml vs 4.402 ng/ml, $P = 0.047$). In our study, we noticed higher values vs reference ranges in nodular goitre group (mean 5.046 (2.28–7.81) ng/ml vs 0.54 (0–2.28) ng/ml, $P < 0.0001$). However, serum Gal-3 did not discriminated between different PTC stages. Intra-assay cv% in our hands was 3.57%.
Conclusion
Serum Gal-3 might be considered as an early circulating tumour marker in thyroid cancer. Our preliminary data showed no association of serum Gal-3 with tumour aggressiveness.
Disclosure
UEFISCDI grant PN-II- PT-PCCA-2011-3.2 no.135/2012.

DOI: 10.1530/endoabs.37.EP866

EP867

The two tyrosine kinase inhibitors, CLM29 and CLM3, have antineoplastic activity in primary cultures from anaplastic thyroid cancer obtained from fine needle aspiration

Silvia Martina Ferrari[1], Poupak Fallahi[1], Concettina La Motta[2], Gabriele Materazzi[3], Francesca Ragusa[1], Francesca Limongi[1], Ilaria Ruffilli[1], Federico Da Settimo[2], Paolo Miccoli[3] & Alessandro Antonelli[1]
[1]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [2]Department of Pharmacy, University of Pisa, Pisa, Italy; [3]Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy.

Anaplastic thyroid cancer (ATC) is one of the most lethal endocrine malignancy, with a mean survival of about 6 months. Until now, the most effective therapy for ATC comprises a multimodal treatment protocol, including surgery, chemotherapy (doxorubicin and cisplatin), and hyperfractionated accelerated external beam radiotherapy, with a median patient survival of 10 months. A possible increase in the effectiveness of the treatment could be achieved testing the sensitivity of 'primary anaplastic thyroid cancer cells' (pATC) from each subject to different drugs, in this way avoiding the administration of inactive therapeutics to these patients. Here, we tested the *in vitro* antineoplastic effect of the two new 'pyrazolo (3,4-d) pyrimidine' compounds (CLM3, CLM29) in pATC obtained both from

biopsy (biop-pATC), or from fine needle aspiration (FNA-pATC), from five patients. We evaluated different concentrations of both compounds (1, 10, 30, and 50 μM). A significant reduction of proliferation was evidenced in FNA-pATC, or biop-pATC, cells by WST-1 assay (a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide, used in the MTT assay) with respect to the control, especially with CLM29, while slightly with CLM3. Furthermore the percentage of apoptotic cells in FNA-pATC, or biop-pATC, cells was increased dose-dependently by both compounds. Our results show no significant differences in sensitivity to CLM29 or CLM3 between the tested ATC cells from FNA, or biopsy.We conclude that: 1) primary FNA-pATC cells have a sensitivity to tyrosine kinase inhibitors (TKIs) agents quite similar to that observed in biop-pATC cells, and for this reason the use of primary FNA-pATC cells to conduct the *in vitro* tests could reduce the time needed for biopsy; 2) CLM29 and CLM3 reduce cell growth, increasing the percentage of apoptotic cells in ATC; 3) the possibility to test sensitivity to different TKIs in each patient could increase the efficacy of treatments, avoiding the administration of ineffective drugs.

DOI: 10.1530/endoabs.37.EP867

EP868

Role of miR-26a in follicular thyroid carcinoma

Erica Gentilin[1,2], Elisa Ortolan[1], Teresa Gagliano[1], Carmelina Di Pasquale[1], Simona Falletta[1], Roberta Rossi[1], Katiuscia Benfini[1], Federico Tagliati[1], Ettore Degli Uberti[1,2] & Maria Chiara Zatelli[1,2]
[1]Department of Medical Sciences, University of Ferrara, Ferrara, Italy; [2]LTTA, Laboratorio per le Tecnologie delle Terapie Avanzate, Ferrara, Italy.

Follicular thyroid carcinoma (FTC) is the second most common thyroid malignant epithelial tumor. It is clinically asymptomatic, usually represented by a single nodule, less often multiple, with origin from thyroid follicular epithelial cells. Despite its well-differentiated characteristics, FTC may develop distant metastases through hematogenous dissemination. The molecular alterations involved in the pathogenesis of follicular neoplasia are not completely known. Recent studies have demonstrated the importance of miRNAs, small non-coding nucleic acids that regulate gene expression at post-transcriptional level. It is well known that the expression profile of miRNAs is altered in follicular thyroid carcinoma. To date, the aftermaths of deregulated expression of miRNAs in the FTC have not been clarified. In order to investigate the molecular mechanisms involved in thyroid tumorigenesis, we evaluated the effects of miR-26a modulation in a human FTC cell line. We observed that miR-26a is significantly down-regulated in FTC-133 cells as compared to a thyroid normal cell line, NTHY-ORI. Our results demonstrated that miR-26a does not directly regulate Protein Kinsae C Delta (PRKCD), a known target of this miRNA, but influences its levels. PRKCD is a regulator of caspase-mediated apoptosis, vascular endothelial growth factor (VEGF)-mediated cell proliferation and iodide uptake *via* sodium iodide symporter (NIS). We observed that miR-26a up-regulation increases PRKCD and NIS protein levels as well as caspase activity, but does not influence VEGF secretion. These results support the hypothesis that miR-26a may influence thyroid differentiation processes and nay represent a therapeutic target for future innovative therapy in advanced radio-refractory disease.

DOI: 10.1530/endoabs.37.EP868

EP869

A rare case of an off midline thyroglossal duct cyst papillary thyroid carcinoma

Melania Balas[1], Ioana Golu[1], Daniela Amzar[1], Mihaela Vlad[1], Emilia Ianes[2], Alis Dema[3] & Ioana Zosin[1]
[1]Department of Endocrinology, University of Medicine and Pharmacy V. Babes, Timisoara, Romania; [2]Department of Oral and Maxillofacial Surgery, University of Medicine and Pharmacy V. Babes, Timisoara, Romania; [3]Department of Morphopathology, University of Medicine and Pharmacy V. Babes, Timisoara, Romania.

Introduction
Papillary thyroid carcinoma can be found very rarely in a thyroglossal duct cyst (TDC) (1%), this cancer variant being the most common type. Although, most of the TDC develop in the midline of the thyroglossal duct (∼70%), some cysts occur off midline, within 2 cm of the midline.
Case presentation
The female patient of 34-year-old presented at the Maxillofacial Surgery Department in October 2014, with a right submandibular painless neck mass at about 1.5 cm of the midline. The lump was discovered by the patient during pregnancy and increased in size gradually, reaching 2.5 cm at 5 months after birth. The clinical examination did not reveal any pathological aspects of the thyroid, nose, nasopharynx, or cervical lymph nodes. The ultrasound of the swelling revealed a pseudosolid mass near the hyoid bone, with thick capsule (4 mm), microcalcifications, and internal vascularity. The post-contrast computed tomography (CT) showed a 28/23 mm right submandibular mass, with complex heterogeneous composition, thick capsule, several microcalcifications in the solid component, no adenopathies, and no surrounding infiltration. After the mass was removed, histological examination established the diagnosis of papillary thyroid carcinoma. Subsequently, the evaluation of the thyroid gland (ultrasound, functional tests, and scintigraphy) detected no abnormalities. Up to now, the patient (still breastfeeding) has been closely monitored by clinical examination and thyroid ultrasound. Suppressive thyroxine treatment will be taken further into discussion.
Discussion and conclusions
As TDC in adults presents variable sonographic and CT appearance, the diagnosis poses sometimes difficulties. Moreover, the diagnosis can be hampered by the unusual off line location of the TDC. The management of the TDC carcinoma is still controversial, the recommendations ranging from only Sistrunk procedure to total thyroidectomy, followed by radioiodine and suppressive thyroxine treatment, or only suppressive doses of thyroxine.

DOI: 10.1530/endoabs.37.EP869

EP870

Chemotherapy effectiveness in the treatment of non-medullary well-differentiated thyroid cancer: a systematic and case review

Ana Albero[1], Esther Martín[2], Alberto Torres[3], Teresa García[1], Natividad Gonzalez[3], María de Carmen del Alamo[1], Luis de la Cruz[1] & Tomás Martín[3]
[1]Department of Oncology, Hospital Virgen Macarena, Seville, Spain; [2]Andalusian Agency for Health Technology Assessment, Seville, Spain; [3]Department of Endocrinology and Nutrition, Hospital Virgen Macarena, Seville, Spain.

Introduction
Nowadays, use of chemotherapy in well-differentiated non medullary thyroid cancer, locally advanced stage and/or with radioiodine-refractory metastases is considered of scanty value. However, in the last 40 years was not published any phase III study nor a systematic review of its use in clinical setting.
Methods
A systematic literature search was performed in databases such as Medline and Embase, among others. Two independent reviewers analysed the articles selected full text, made a critical reading and extracted results using forms designed specifically. A qualitative synthesis of the results was performed and the accumulated data were calculated.
Results
A total of 509 references were found. Sixteen studies involving 473 patients published were included. Thirteen studies showed individual response data to treatment. Finally, 179 patients treated with different chemotherapy alone or in combination were identified. The overall response rate (IR) was 27% (0–57%), with a 4% of patients showed a complete response (CR) and clinical benefit (CB) in 60% (14–100%). Eight studies reported data response relative to histologic subtype. The IR for the 37 cases with papillary cancer was 24% (0–50%) and 32% (5% CR) (0–100%) of 56 with follicular cancer. However, data must be interpreted carefully due to the risk of bias detected. Unlike modern studies a performance status >2 was described in about 40% of patients. Five individual studies published survival data from 54 patients with advanced CDT: the median survival was estimated at 18 months (95% CI 0–37.5), with significant differences between patients treated before 2000 vs those treated later (7 months vs 41 months, $P<0.00$).
Conclusion
There are insufficient data to evaluate the effectiveness of chemotherapy in patients with advanced non-medullary thyroid cancer, although, it seems to have some efficacy, therefore, it could be necessary to be tested in well-designed studies vs or in combination with new therapies.

DOI: 10.1530/endoabs.37.EP870

EP871

Other malignancies accompanying differentiated thyroid cancer in Turkish Cypriots: a single-centre study

Sebnem Aydin[2], Umut Mousa[1], Osman Koseoglulari[1] & Hasan Sav[1]
[1]Department of Endocrinology and Metabolism, B Nalbantoglu Hospital, Nicosia, Cyprus; [2]Department of Nuclear Medicine, B Nalbantoglu Hospital, Nicosia, Cyprus.

Introduction
The aim of this study was to determine the frequency and types of accompanying malignancies in Turkish subjects with differentiated thyroid cancer (DTC) residing in the northern region of Cyprus.
Subjects and methods
We retrospectively analysed 567 subjects with a diagnosis of DTC in the Departments of Endocrinology and Nuclear Medicine.
Results
Four hundred and forty-eight (79%) were females and 119 (21%) were males. A total of 17 subjects (2.9%) had an accompanying second malignancy other than DTC. Sixteen were females (94.2%) and one was male (5.8%). The mean age was 46.3 years for subjects with DTC being the only malignancy and 54.76 years for those with accompanying malignancies ($P<0.05$). Out of these 17 subjects 14 had classical papillary thyroid cancer (PTC), two had PTC follicular variant, and one had follicular thyroid cancer. All subjects received radioactive iodine for remnant ablation. The secondary malignancies were breast cancer in nine subjects (52.9%), endometrium cancer in two subjects (11.7%) and acute lymphoblastic leukemia, Hodgkin lymphoma, lung cancer, malignant melanoma, and gastrointestinal stromal tumour in one subject each. In 11 subjects DTC developed secondarily, in five subjects DTC developed first and in one subject DTC and the other malignancy developed synchronously.
Conclusion
The rate of accompanying malignancies in DTC was 2.9%. Classical PTC was the most frequent tumour type accompanying other malignancies (82.3%). DTC was observed four times higher in female subjects compared to male subjects. The role of gender was higher in those with accompanying malignancies. The most frequently observed accompanying malignancy was breast cancer leading by far. Only five subjects had developed a malignancy after the diagnosis of DTC and 12 subjects had a diagnosed malignancy before DTC. Thus we believe the role of RAI remnant ablation for secondary malignancy development is none or minimal.

DOI: 10.1530/endoabs.37.EP871

EP872

Role of thyroglobulin as a predictor of the evolution of disease in differentiated thyroid cancer

Betina Biagetti, Carles Zafón, Amparo García-Burillo, Mónica Velasco, Gabriel Obiols, Joan Castell & Jordi Mesa
Vall d'Hebron Hospital, Barcelona, Spain.

Aim
Investigate, in patients with differentiated thyroid cancer (DTC) if thyroglobulin (Tg) values, immediately before and six months post radioiodine ablation are good predictors of disease progression.
Materials and methods
Basal Tg values (Tg-B) and rhTSH stimulated Tg (Tg-S) before ablation (0) and 6 months later (6) from 142 DTC patients, with post-surgical ablation therapy between 2003 and 2009 with a follow up of 5 years, were analysed.
Results
After a 5-year follow up, 121 patients (85.2%) were free of disease (FD), 15 patients (10.6%) had evidence of disease (ED) and six had died (4.2%). A Tg-B-0 <0.2 ng/ml. was present in 39 patients (27.5%), only one (2.5%) has ED because of positive antibodies and only one (2.5%) needed retreatment. In contrast: a Tg-B-0 >0.2 ng/ml, was present in the 103 patients (72.5%), 21 patients (20.4%) had ED and 27 (26.2%) needed retreatment A Tg-S-0 <1 ng/ml was found in 34.8% only one (2.6%) was ED and only one (2.6%) required retreatment. However, 65.2% of patients had these value >1 ng/ml, of which 22.5% was considered ED and 26.7% have required retreat. At 6-month when Tg-B-6 ablation >0.2 ng/ml, 40% was ED and 46.7% required retreatment and when Tg-S-6-ablation >1 ng/ml, 56% was ED, and 67% required retreatment in 5 years follow up.
Conclusion
Tg basal value at the time of ablation has a high specificity and sensitivity for predicting disease progression. Stimulated Tg at that time does not add predictive value At 6-month high levels of Tg value predicts evidence of disease in 5 years follow up.

DOI: 10.1530/endoabs.37.EP872

EP873

Clinical and biological differences between incidental and non-incidental papillary thyroid microcarcinomas

Miguel Paja[1], Eider Etxebarria[1], Ma Teresa Gutiérrez[2], Amaia Expósito[2], Maddalen Dublang[1], Amelia Oleaga[1], Maite Pérez de Ciriza[1] & Aitziber Ugalde[3]
[1]Endocrinology Department, Hospital Universitario de Basurto, Bilbao, Basque Country, Spain; [2]Endocrine Surgery Department, Hospital Universitario de Basurto, Bilbao, Basque Country, Spain; [3]Pathology Department, Hospital Universitario de Basurto, Bilbao, Basque Country, Spain.

The clinical significance and potential morbidity of papillary thyroid microcarcinomas (PTMC) is discussed. Particularly the differences between those PTMC identified postoperatively in histological examination (incidentals), and those diagnosed preoperatively (non-incidentals). We retrospectively analysed differences in clinical presentation and course after treatment in these two groups. The study population consisted of 199 patients with PTMC who underwent surgery from 2000 to 2014. Eight patients preoperatively diagnosed of lateral compartment lymph node metastasis (LNM) were excluded, as they were considered suffering a more advanced disease. We compared characteristics, and outcomes between both groups. There were 118 incidental and 73 non-incidental PTMC. Patients with Incidental PTMC were older (55.7 years vs 50.8 years; $P=0.01$), have smaller tumours (4.3 mm vs 7.9 mm; $P=0.001$) and lower preoperative TSH (1.87 vs 3.06; $P=0.001$). Incidence of serological or histological evidence of autoinmunity was not different between both groups. Multifocal disease (46.8% vs 29.8%; $P=0.02$) and extracapsular invasion (25.6% vs 4%; $P<0.001$) were most frequently reported in non-incidental neoplasms. One hundred and sixteen out of 122 patients treated with radioiodine had at least 1 year of follow-up (62 incidentals and 54 non-incidentals). One year after radioiodine, eight incidental cases didn't reach remission criteria (undetectable stimulated thyroglobulin and normal high-resolution cervical ecography). Three of them persisted with biochemical disease 1, 2, and 3 years passed, one patient is waiting for surgery to identified cervical adenopathy, two achieved remission after ganglionar surgery plus more radiodine and two without additional treatment. There were two non-incidental patients without remission 1 year after ablation, both without structural disease, persistent 1 and 6 years passed. There was one biochemical relapse after initial remission in the non-incidental group. In our series, incidental and non-incidental PTMC showed differences at presentation, but similar biological behavior in the follow-up after treatment. Remnant disease is more often seen in incidental carcinomas after ablation.

DOI: 10.1530/endoabs.37.EP873

EP874

Differentiated thyroid cancer: tendency changes from 1970 to 2012 in the southwest of Spain

Antonio Jesús Martínez Ortega[1], Elena Navarro González[1], Raquel Guerrero Vázquez[1], Ana de los Reyes Romero Lluch[1], José Manuel Martos[2] & Ignacio Cuenca Cuenca[3]
[1]Endocrinology Department, Virgen del Rocío University Hospital, Seville, Spain; [2]Endocrine Surgery Department, Virgen del Rocío University Hospital, Seville, Spain; [3]Nuclear Medicine Department, Virgen del Rocío University Hospital, Seville, Spain.

There is a specific unit specialised in treating differentiated thyroid cancer (DTC) at the Endocrinology Department from a hospital the southwest of Spain that attends patients from two different provinces. Owing to environmental pollution, one of them has higher incidence of cancer.
To evaluate the changes in the clinical presentation of DTC over time and analyse possible differences between patients from the two provinces, we designed a descriptive retrospective study, including all DTC cases admitted from January 1970 to March 2014. Quantitative variables are expressed as median (interquartile range). All the results were standardized using specific population records from the National Institute for Statistics for each time period.
Results
Total population 1289 (255 males/1034 females). Age at diagnosis: 43 years (33–55); 82.2% were papillary thyroid cancer (PTC) while 17.5% were follicular thyroid cancer (FTC). We found a progressive increase in PTC since 1970, more marked from 1996 to the present in both sexes (mainly between 21 and 65 years at diagnosis), in tumours >1 cm (T1b-T4), as well as papillary microcarcinoma, following the same trend. A similar pattern was observed in FTC. There were no differences regarding unfavourable histological subtypes. In the 1970's, PTC and

FTC tended to be >4 cm and/or with extrathyroid extension, N1 and M1, in comparison with the current presentation (<4 cm, limited to the thyroid and N0 M0). In patients from the most polluted province we detected a non-significant slightly higher percentage of high-risk tumours (8.85% vs 7.55%) without any other differences.

Conclusion

DTC clinical presentation has shifted from high-risk tumours at diagnosis (1970's and 1980's) to a low-risk profile (T1-3, N0, and M0) in the last years, with a steadily increase in the number of cases per year, mainly PTC. Men have a tendency to have higher risk tumours than women.

DOI: 10.1530/endoabs.37.EP874

EP875

Thyroid cytology–biopsy correlation

Inmaculada Gavilán-Villarejo[1], Laura Larrán-Escandón[1], Isabel Mateo-Gavira[1], Pilar Roldán-Caballero[1], Cristina López-Tinoco[1], Diego Martínez-Parra[2], Eduardo Vallejo-Roca[3] & Manuel Aguilar-Diosdado[1]
[1]Endocrinology, Puerta del Mar Hospital, Cádiz, Spain; [2]Pathological Anatomy, Puerta del Mar Hospital, Cádiz, Spain; [3]Radiology, Puerta del Mar Hospital, Cádiz, Spain.

Background

Fine-needle aspiration (FNA) biopsies are the cornerstone of preoperative evaluation of thyroid nodules, but FNA diagnostic performance has varied across different studies. We conducted a study to evaluate the effectiveness of ultrasound guided FNA in the thyroid nodule and to review the correlation between cytopathology and histopathology.

Methods

Prospective FNAs were collected from 332 patients who underwent thyroid surgery between 2008 and 2013. The cytological sample was assessed by a single consultant pathologist and was classified as inadequate, non-neoplastic, neoplastic, or indeterminate. The histology were classified as non-neoplastic (benign), neoplastic (malignant). Sensitivity, specificity, positive predictive value, and negative predictive value were calculated.

Results

The mean age was 51.65 ± 13.40 years, 279 (84%) were women. The average size of nodules was 3.35 ± 1.41 cm. Multinodular goiter presented with dominant nodule 239 (72%) patients and 93 (28%) single nodule. Cytology analysis showed 216 (66.3%) benign, 86 (26.4%) indeterminate, and 24 (7.4%) malignant. One hundred and ninety-seven (59.3%) patients underwent total thyroidectomy. From this population indeterminate cytology rate were 75 (87.2%) benign and 11 (12.6%) malignant histopathology. The FNAs had a sensitivity of 84.62%, specificity of 99.07%, positive predictive value of 91.67%, and negative predictive value 98.15%.

Conclusions

Ultrasound-guided FNA provides important information for the diagnosis and the preoperative evaluation of thyroid nodules. The low rate of false-positive and false-negative results suggests that it might be enough for surgical planning for thyroid nodule.

DOI: 10.1530/endoabs.37.EP875

EP876

Simultaneous occurrence of different follicular neoplasms within the same thyroid gland: a retrospective study

Sefika Burcak Polat[1], Dilek Arpaci[2], Aylin Kilic Yazgan[3], Husniye Baser[1], Mehmet Kilic[4], Reyhan Ersoy[1] & Bekir Cakir[1]
[1]Endocrinology and Metabolism Department, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey; [2]Enocrinology and Metabolism Department, Karaelmas University Hospital, Zonguldak, Turkey; [3]Pathology Department, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey; [4]General Surgery, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey.

Introduction

Neoplasms of the thyroid gland are classified according to the cell that it originates and commonly they originate from follicular or parafollicular C cells. The most common differentiated thyroid cancers (DTC) are papillary and follicular carcinomas. Coexistence of two different histological types of primary follicular thyroid neoplasm is a rare condition. There are previous reports of concomitant medullary and papillary thyroid cancers. However, there is scarce data about the simultaneous two different histological types of primary follicular thyroid tumors and this is the first study on that subject.

Method

From January 2007 to September 2014, our institutional database was reviewed for patients who underwent thyroid surgery for various indications. Medical records and cytopathology reports of those patients were examined retrospectively. Simultaneous neoplasms of follicular origin were noted.

Results

A total of 3700 patients were operated. Histopathological examination result was benign in 2686 (73%) patients while it was malignant in 1014 (27%) patients. Among the patients with the diagnosis of DTC only 20 (1.9%) had accompanying second neoplasia within the same thyroid gland. PTC had thyroid capsule invasion in seven patients (35%) while capsule was intact in 13 (65%). In 17 (85%) patients there wasn't vascular invasion whereas in three patients (15%) vascular invasion was detected in PTC. Second neoplasm was follicular carcinoma in ten patients, Hürthle cell carcinoma in two patients, Hürthle cell adenoma in five patients, and follicular adenoma in three patients.

Conclusion

Such simultaneous tumors may be part of a familial tumour syndrome or an unidentified novel gene mutation playing role in the pathogenesis of more than one type of tumor. Based on the current evidence the synchronous occurrence of those neoplasms in a given patient is likely coincidental in the literature. Further study is required using a larger patient population with standardised genetic characterisation.

DOI: 10.1530/endoabs.37.EP876

EP877

Thyroid Imaging Reporting and Data System (TIRADS) can reduce the needed number of FNA

Dana Stoian[1,5], Mihnea Derban[2], Florian Varcus[3], Bogdan Timar[6] & Mihaela Craciunescu[4]
[1]Department of Obstetric Gynecology, Victor Babes University of Medicine, Timisoara, Romania; [2]Department of Pathology, Victor Babes University of Medicine, Timisoara, Romania; [3]Department of Surgery, Victor Babes University of Medicine, Timisoara, Romania; [4]Department of Microbiology, Victor Babes University of Medicine, Timisoara, Romania; [5]Center for Elastography, Timisoara, Romania; [6]Department of Medical Informatics, Victor Babes University of Medicine, Timisoara, Romania.

The prevalence of solid thyroid nodules is very high in the general population. Appropriate selection of cases for surgery is the most important task, when evaluating nodules. The present study wants to see if the use of Thyroid Imaging Reporting and Data System (TIRADS) could decrease the number of needed FNAB procedures.

Material and method

174 nodules evaluated by conventional ultrasound and real time elastography, with linear multifrequency probe, Hitachi Preirus Machine, Hitachi, Inc. Prospective all nodules were classified by TIRADS system: ecogeneity (risk = inhomogeneity), margins (risk = irregular margins), shape (risk = irregular shape, taller than wide), calcification (risk = micro calcifications), lymph node (risk = presence), and increased strain (color map 4, 5, increased strain ration). TIRADS 4A, 4B, and 5 cases were referred also to FNAB. All 174 cases were operated and pathology report was obtained.

Results

Cancer was certified in 29 of the 174 operated thyroid nodules. The number of required punctions would be in 169 cases, if we consider the AACE guidelines. If we apply the TIRADS system (all 4A, 4B, and 5 TIRADS nodules) in selecting the cases for FNAB, the number would decrease significantly up to 74 nodules. The diagnostic quality of TIRADS is very high: using the ROC method, the AUC = 0.95761, confidence limit of 0.8424–0.989 (95% LCL and 95% UPL). The sensitivity and specificity in diagnostic of cancer was excellent: diagnostic sensitivity, 86.20% with high specificity, 97.24%, with the best accuracy of 95.40%.

Conclusion

Using TIRADS system, the correct evaluation of the majority of the thyroid nodules is achieved.

DOI: 10.1530/endoabs.37.EP877

EP878

Female male ratio in thyroid cancer

Sevilay Ozmen[1], Ilknur Calik[1], Aynur Arslan[1], Ozge Timur[2], Hakan Sevimli[2], Ayse Carlioglu[3], Senay Arikan Durmaz[3], Ali Kurt[1] & Fazli Erdogan[1]
[1]Department of Pathology, Training and Research Hospital, Erzurum, Turkey; [2]Department of Internal Medicine, Training and Research Hospital, Erzurum, Turkey; [3]Department of Endocrinology, Training and Research Hospital, Erzurum, Turkey.

Aim
402 patients who were admitted and FNA was done in the Endocrinology Clinic at EBEAH were enrolled in this study. 340 (85%) of them were females and 62 (15%) of them were males. The age range was between 16 and 82. There weren't any statistical differences in age between both sexes. Thyroid cancer is reported to constitute $<2\%$ of cancers in humans. At the same time, it is the most lethal endocrine malignancy. In the literature it is stated that 3% of all cancers in women and 1% of all cancers in men is thyroid cancer. Papillary thyroid carcinoma is the most common malignant neoplasm of thyroid, it generates $\sim$80% of all thyroid cancers.
Results
340 of the examined 402 cases were female and cytopathological results of 303 (89.11%) were benign, 37 (10.88%) were malignant. A total of 62 male patients, 55 (88.70%) were benign, 7 (11.29%) were malignant. Totally 358 cases were reported as benign, 44 cases were reported as malignant. Of the 37 patients who were female, 26 had malignant papillary carcinoma, eight had papillary microcarcinoma, and three had follicular carcinoma. Of the seven male cases which were histopathologically reported as malignant, four had papillary carcinoma, two had papillary microcarcinoma, and one of them was reported as a well-differentiated neoplasm of uncertain malignant potential. When the results of FNAB were analysed according to the gender distribution, there wasn't any statistically significant difference. The results of FNAB were reported as benign in 89.11% of female and 88.70% of male patients. The positive assessment in terms of malignancy were 10.88% in females and 11.29% in males. Although, some malignancies are more common in women and some in men, thyroid malignancies can develop at any gender. In this study which includes 402 cases there was no significant difference in terms of gender. And these findings are very close to the values reported in the literature.

DOI: 10.1530/endoabs.37.EP878

EP879

Histhopathological verification of atypia of undetermined significance in Bethesda system

Sevilay Ozmen[1], Ilknur Calik[1], Ahmet Erkan Bilici[1], Ozge Timur[2], Ayse Carlioglu[3], Senay Arikan Durmaz[3], Fazli Erdogan[1] & Ali Kurt[1]
[1]Department of Pathology, Training and Research Hospital, Erzurum, Turkey; [2]Department of Internal Medicine, Training and Research Hospital, Erzurum, Turkey; [3]Department of Endocrinology, Training and Research Hospital, Erzurum, Turkey.

The pathologist cannot easily decide some thyroid fine-needle aspiration biopsy (FNA) into the benign, suspicious, or malignity and this condition are reported as 'atypia of undetermined significance' (AUS) or 'follicular lesion of undetermined significance' in the Bethesda system. Diagnosis of AUS of a thyroid nodule is leaved an endocrinologist as well as the patients in a difficult situation. However, the risk of malignancy at AUS is $\sim$5–15%. Our aimed to this study is to determined histhopathological verification of atypia of undetermined significance according to Bethesda system.
Materials and methods
Results of FNA were used totally in 402 patients with nodular goitre from our hospital records from 2012 to 2014. Twenty people (19 women and one man) out of this study population were diagnosed AUS. All the patients had undergone total or subtotal thyroidectomy. We retrospectively re-evaluated postoperative biopsy results and compared with those histhopathological diagnoses.
Results
It was found that postoperative biopsy results of the patients who were diagnosed AUS were adenomatous hyperplasia (5%, $n=1$), nodular goitre (65%, $n=14$), papillary carcinoma (5%, $n=1$), Hashimoto's thyroiditis (15%, $n=3$), and microfolliculary adenoma (5%, $n=1$).
Conclusions
Our finding demonstrated that AUS category substantially indicated to benign cellular change. This date was found in accordance with prediction of Bethesda system. Therefore, a repeated FNA should be performed after an appropriate period of time. The factors including follicular lesion in part suspicious follicular neoplasia, existence of lymphoid cell, hypocellularity and artefact of sample preparation may lead to misdiagnosis of malignity in patients with AUS.

DOI: 10.1530/endoabs.37.EP879

EP880

A pitfall of thyroid fine-needle aspiration biopsy results

Sevilay Ozmen[1], Ilknur Calik[1], Emre Akarsu[1], Ozge Timur[2], Ayse Carlioglu[3], Hakan Sevimli[2], Senay Arikan Durmaz[3] & Ali Kurt[1]
[1]Department of Pathology, Training and Research Hospital, Erzurum, Turkey; [2]Department of Internal Medicine, Training and Research Hospital, Erzurum, Turkey; [3]Department of Endocrinology, Training and Research Hospital, Erzurum, Turkey.

Introduction and aim
Bethesda system for thyroid cytopathology has been widely used recently. Approximately 3–7% of thyroid fine-needle aspiration (FNA) biopsy is considered as malign. Suspicious or malign nodules should likely to be resected. Aim of this study is to confirm the diagnosis of malign or suspicious for malignity according to Bethesda classification in patients with nodular goitre after thyroidectomy.
Materials and methods
Results of FNA in totally 402 patients with nodular goitre were achieved from our hospital records. All of the patients had undergone totally or subtotals thyroidectomy. We re-evaluated retrospectively biopsy results postoperatively. We compared their preoperative FNA results.
Results
We described totally five patients whom FNA were malignity but results of postoperative biopsy were benign. We found false positive results as one 38-year-old patient with follicular adenoma, one 50-year-old patient with papillary thyroid cancer, and three patients (44.6 ± 8.7 years) with suspicious for papillary thyroid cancer.
Conclusions
The malignity risk in classification of suspicious for malignity and malignity according to Bethesda reporting system is 60–75 and 97–99% respectively after thyroidectomy. Our findings demonstrate that our false positive results are lower than reported Bethesda classification in medically literature. Hyperplastic adenomatoid nodule, follicular adenoma, well-differentiate follicular carcinoma and papillary carcinoma follicular variant have several characteristic features in common. Therefore, difficulty of these lesions in pathologically evaluation may lead false positive results.

DOI: 10.1530/endoabs.37.EP880

EP881

Histopathology results of follicular neoplasia according to Bethesda classification in thyroid fine-needle aspiration biopsy

Sevilay Ozmen[1], Ilknur Calik[1], Ebru Sener[1], Ozge Timur[2], Ayse Carlioglu[3], Hakan Sevimli[2], Senay Arikan Durmaz[3] & Ali Kurt[1]
[1]Department of Pathology, Training and Research Hospital, Erzurum, Turkey; [2]Department of Internal Medicine, Training and Research Hospital, Erzurum, Turkey; [3]Department of Endocrinology, Training and Research Hospital, Erzurum, Turkey.

Introduction and aim
Interpretation of follicular neoplasia classification according to Bethesda system in thyroid fine needle aspiration biopsy is very different among pathologist. A number of definition including 'follicular lesion', 'follicular proliferation', 'follicular lesion of undetermined significance', and 'follicular neoplasia' were used in terminology. A clearly discrimination between nodular goitre, follicular adenoma, and follicular carcinoma cannot lack due to same cytomorphologic features. Approximately 15–30% of case of follicular neoplasia in thyroid fine-needle aspiration biopsy (FNA) is considered as malignity. Aim of this study is to confirm with histopathological diagnosis after thyroidectomy in patients with follicular neoplasia according to Bethesda classification.
Materials and methods
Results of FNA in totally 402 patients with nodular goitre were achieved from our hospital records from 2012 to 2014 years. All the patients had undergone totally or subtotal thyroidectomy. We retrospectively re-evaluated postoperatively biopsy results.
Results
We described ten patients whom diagnosis of FNA were follicular neoplasia but results of postoperative biopsy were found adenomatous nodule ($n=1$),

'adenomatous nodule and chronic lenfocytic thyroiditis' ($n=1$), 'papillary carcinoma', 'follicular variant ($n=2$)', 'nodulary goitre' ($n=4$), 'adenomatous nodule-Hürthle cell variant ($n=1$)', and 'well-differentiated follicular neoplasia'.
Conclusions
Our finding demonstrated that descriptive criteria of folliculary neoplasia in FNA substantially point out hyperplastic proliferation rather than neoplasia.

DOI: 10.1530/endoabs.37.EP881

EP882

The rare intracellular RET mutation p.S891A in a Turkish family with hereditary medullary thyroid carcinoma

Caglar Keskin & Sevim Gullu
Department of Endocrinology and Metabolic Disease, Ankara University Faculty of Medicine, Ankara, Turkey.

Introduction
Medullary thyroid carcinoma (MTC) could be familial in 30% of cases. Here, we report a family of FMTC with rarely seen RET p.S891A mutation.
Case presentation
A 49-year-old man presented with a single nodule in the left lobe of thyroid. Thyroid ultrasonography (US) showed a nodule and pathological cervical lymph nodes. There was no relevant family history. Fine-needle aspiration cytology (FNAC) of the nodule was consistent with a diagnosis of medullary thyroid carcinoma. Serum calcitonin level was 906 pg/ml (reference range 0–18) and the other laboratory tests, parathyroid hormone level and 24-h urine catecholamine levels were normal. An extensive RET molecular analysis identified the rare intracellular RET p.S891A mutation. Then the patient underwent total thyroidectomy and bilateral neck dissection. Histopathology revealed medullary thyroid carcinoma pT1bN1bM0 with capsular and lymphovascular invasion and lymph node metastases. Serum calcitonin and carcinoembryonic antigen levels measured 3 months after the surgery was 569 pg/ml and 12 ng/ml respectively. During the follow-up there was progressive rise in calcitonin and CEA levels. No distant metastases were detected. Since there were cervical pathological lymph nodes he was planned to have revision operation. RET p.S891A mutation was also detected at his daughter. She was completely asymptomatic and baseline serum calcitonin level was normal. Calcium stimulation test showed no marked increase in CT levels therefore prophylactic thyroidectomy was postponed.
Conclusions
We reported a patient who presented all characteristic features of sporadic MTC but extensive molecular analysis revealed rarely seen intracellular RET p.S891A mutation and his daughter had same mutation. RET genetic screening is very important tool for the preclinical diagnosis and early treatment of unsuspected affected family members.

DOI: 10.1530/endoabs.37.EP882

EP883

Aggressive medullary thyroid cancer in a homogenous population

Paul Lennon[1], Sandra Deedy[2], Andrew Green[3], John Kinsella[1], Conrad Timon[1], James Paul O'Neill[4] & Marie-Louise Healy[1]
[1]St. James's Hospital, Dublin, Ireland; [2]National Cancer Registry, Cork, Ireland; [3]National Centre for Medical Genetics, Dublin, Ireland; [4]Royal College of Surgeons, Dublin, Ireland.

Introduction
Medullary thyroid cancer arises from the calcitonin-secreting parafollicular C cells and consists of a spectrum of disease that ranges from extremely indolent tumours, where patients may survive for many years with a large tumor burden, to aggressive types associated with a high mortality rate. The objective of our study is to evaluate the prognostic factors and outcomes of patients diagnosed with medullary thyroid cancer in a homogenous population, and to examine the tissue sample of patients diagnosed with MTC for mutations in the RET proto-oncogene from the same period.
Methods and design
A retrospective analysis of the National Cancer Registry in Ireland was undertaken, for patients with a diagnosis of medullary thyroid cancer between 1998 and 2007. The Kaplan–Meier method was used to determine overall survival and factors predictive of outcome were determined by univariate and multivariate analysis by Cox regression using STATA 13 Software.
Results
Forty-six patients were diagnosed with MTC, 55.8% were females and 44.2% were males. A median age of 52was found. The overall median survival was 6.32 years and the 1- and 5-year overall survival was 88.37 and 62.79% respectively, with a 10-year survival calculated at 48.63%. On univariate analysis age, stage and surgical intervention were statistically significant indicators of prognosis. T stage and age remained statistically significant indicators of prognosis on multivariate analysis. Two patients with no history of MEN syndromes or family history of MTC had RET proto-onocogene mutations.
Conclusions
Our patient cohort was substantially older than what is commonly seen in the literature. There was a very low pick up of RET mutations in sporadic MTC in our patient cohort, and along with relatively poor outcomes, this suggest that further studies of this population may allow us to identify aggressive variants of medullary thyroid cancer.

DOI: 10.1530/endoabs.37.EP883

EP884

Simultaneous occurrence of medullary and papillary thyroid microcarcinomas: case report

Krisztian Sepp[1], Eva Csajbok[1], Sandor Magony[1], Laszlo Tiszlavicz[2], Balint Tobias[3], Attila Patocs[4] & Zsuzsanna Valkusz[1]
[1]First Department of Medicine, University of Szeged, Szeged, Hungary; [2]Department of Pathology, University of Szeged, Szeged, Hungary; [3]First Department of Internal Medicine, Semmelweis University, Budapest, Hungary; [4]Second Department of Internal Medicine, Semmelweis University, Budapest, Hungary.

Thyroid cancers represent ~1% of new cancer diagnoses. Thyroid malignancies are divided into papillary carcinomas (80%), follicular carcinomas (10%), medullary carcinomas (5–10%), anaplastic carcinomas (1–2%), and other rare tumours (primary thyroid lymphomas and primary thyroid sarcomas). The main therapeutic options are surgery (mainly total thyreoidectomy), radioiodine treatment, levothyroxine therapy (TSH suppression dose), others (external beam irradiation, chemotherapy, and tyrosine kinase receptor inhibitors). A medical investigation was started with a 60-year-old male patient due to palpable thyroid nodules. The ultrasonography revealed nodules in the isthmus and in both thyroid glands (diameter: 4.0, 2.7, and 2.0 cm) without lymphadenopathy, the fine-needle aspiration didn't show any malignant suspect cytological sign. The patient was euthyroid, the calcitonin level was elevated (38.5 pg/ml, normal: −9.6). Because of the suspicion of medullary cancer we recommended total thyroidectomy. The postoperative histology showed papillary microcarcinoma in the left lobe nodule and medullary microcarcinoma in the right lobe nodule with no affected lymph nodes. Levothyroxine therapy was started at substitutional dose, there was no radioiodine treatment. Now the patient has undetectable calcitonin level and low human thyreoglobuline level (<1 ng/ml) with normal anti-human thyreoglobuline rate without any sign of recurrence or metastasis. Genetic screening was performed: it is negative for RET mutation, the other markers are processing. In our case a simulataneous occurrence of medullary and papillary thyroid microcarcinomas were detected in different nodules of the thyroid gland, the genetic screening is in process. In the literature <80 similar cases were reported (none in Hungary). Owing to the rarity of the occurrence we are reporting our interesting case.

DOI: 10.1530/endoabs.37.EP884

EP885

The utility of basal serum thyroglobulin measurement, using a highly sensitive immunoassay, in the follow up of patients treated for differentiated thyroid cancer

Nigel Glynn[1], Anne Marie Hannon[1], Lauren Schneekloth[1], Ciara De Buitleir[1], Martina Morrin[2], Frank Keeling[2], Clare Faul[3], Mary Leader[4], Arnold D K Hill[5], William Tormey[6], Diarmuid Smith[1], Chris J Thompson[1] & Amar Agha[1]
[1]Department of Endocrinology, Beaumont Hospital and RCSI Medical School, Dublin, Ireland; [2]Department of Radiology, Beaumont Hospital and RCSI Medical School, Dublin, Ireland; [3]Department of Radiation Oncology, Beaumont Hospital and RCSI Medical School, Dublin, Ireland; [4]Department of Histopathology, Beaumont Hospital and RCSI Medical School, Dublin, Ireland; [5]Department of Surgery, Beaumont Hospital and RCSI Medical School, Dublin, Ireland; [6]Department of Chemical Pathology, Beaumont Hospital and RCSI Medical School, Dublin, Ireland.

Introduction
TSH-stimulated serum thyroglobulin (Tg) is used as a sensitive marker for the detection of early recurrence or residual disease following treatment for differentiated thyroid cancer (DTC). However, stimulated Tg, using TSH or thyroid hormone withdrawal, is either costly or cumbersome for patients.
Aim
To compare the performance of basal T_4 suppressed, with stimulated Tg measurement, in the follow up of patients treated for DTC.
Methods
We retrospectively reviewed patients treated for DTC at our institution between September 2011 and September 2014. Data recorded included patient demographics, surgical pathology, and imaging results as well as biochemical parameters. Tg was measured by a highly sensitive immunoassay with a functional sensitivity of 0.1 ng/ml. A stimulated Tg >2 ng/ml was considered significant. Patients with an elevated anti-Tg antibody titre were excluded.
Results
46 stimulated Tg measurements were performed in 41 patients – TNM stages 1 and 2=33 patients; stages 3 and 4=8 patients. Of the 31 tests in which the basal Tg was <0.1 ng/ml, only one (3%) had a stimulated Tg >2 ng/ml; none had radiological evidence of recurrent or residual disease. If the basal Tg was 0.1–0.5 ng/ml, stimulated Tg was >2 ng/ml in 33% of cases.
Conclusion
Undetectable basal Tg measurement, using a highly sensitive Tg assay, together with negative neck imaging, are highly reassuring for remission following treatment for DTC.

DOI: 10.1530/endoabs.37.EP885

EP886

The introduction of endocrinology–radiology MDT meeting significantly reduced inadequacy rates of thyroid fine-needle aspiration in a University Teaching Hospital

Mohamed Ahmed[1], Michael Jeffers[2], John Feeney[3], Pardeep Govender[3], Mark Sherlock[1] & James Gibney[1]
[1]Department of Endocrinology, The Adelaide and Meath Hospital Incorporating the National Children's Hospital (AMNCH), Tallaght, Dublin, Ireland; [2]Department of Histopathology, The Adelaide and Meath Hospital Incorporating the National Children's Hospital (AMNCH), Tallaght, Dublin, Ireland; [3]Department of Radiology, The Adelaide and Meath Hospital Incorporating the National Children's Hospital (AMNCH), Tallaght, Dublin, Ireland.

Introduction
A weekly endocrinology–radiology multidisciplinary (MDT) meeting has been recently introduced in our hospital to discuss indications and suitability of thyroid nodules for fine-needle aspiration (FNA). In a recent 5 years retrospective audit, 80% of thyroids FNAs were performed under ultrasound (US) guidance in our institution with an overall inadequacy (Thy1) rate of 11.1%.
Objectives
The aim of this study was to assess whether such an intervention can improve percentage of FNAs done under US guidance and reduce inadequacy rates.
Methods
A retrospective review of all computerised meeting records held in 2013. Cytological outcomes for those undergone FNA were obtained from pathology laboratory system.
Results
216 thyroid cases were discussed at our MDT meetings between January and December 2013, of those, FNA was recommended in 118 (54.6%), follow-up US thyroid in 39 (18%), and further images (mainly isotope uptake) in 28 (13%) cases. FNA was not indicated in 31 (14.3%) of cases most of them were small (<1 cm), stable, or hot nodules. 113 thyroid nodules were aspirated following MDT discussion. All FNAs (100%) were performed under US guidance with pathology in attendance to review adequacy of samples. The cytology outcomes were as follows: Thy1 (non-diagnostic) in six (5.3%) cases, Thy2 (benign) in 97 (85.8%) cases, Thy3 (follicular lesion/neoplasm) in seven (6.2%) cases, Thy4 (suspicious for malignancy) in one (0.9%), and Thy5 (malignant) in two (1.8%) cases. Inadequacy rate for FNAs performed following discussion at MDT was significantly lower (5.3%) compared to the overall inadequacy rate of 11.1% reported in the previous audit period ($P<0.05$).
Conclusion
The introduction of endocrinology–radiology MDT resulted in a 52.3% reduction of thyroid FNA inadequacy rate. This MDT proved to be a cost effective intervention in reducing inadequacy rate, hence further costs. All thyroid nodules should be discussed at such meeting to assess suitability for FNA.

DOI: 10.1530/endoabs.37.EP886

EP887

Value of neutrophil to lymphocyte ratio in predicting malignancy in thyroid nodules diagnosed as follicular neoplasm on cytology

Neslihan Soysal-Atile[1], Nuray Can[2], Sibel Güldiken[3], Hüseyin Çelik[3], Atakan Sezer[4], Dogan Albayrak[4] & Armagan Tugrul[3]
[1]Endocrinology Department, Tekirdag State Hospital, Tekirdag, Turkey; [2]Pathology Department, Trakya University Faculty of Medicine, Edirne, Turkey; [3]Endocrinology Department, Trakya University Faculty of Medicine, Edirne, Turkey; [4]General Surgery Department, Trakya University Faculty of Medicine, Edirne, Turkey.

Aim
It is well known that there is a strong relationship between chronic inflammation and tumorigenic process. The cytological diagnosis of follicular neoplasm (FN) carries a 20–30% risk of malignancy for thyroid nodules. In this study, we aimed to evaluate whether preoperative neutrophil to lymphocyte ratio (NLR) is a predictive factor for malignancy in thyroid nodules diagnosed as FN on cytology.
Materials and methods
A total of 139 patients with FN who were treated by surgery were enrolled. Preoperative demographic and laboratory findings, USG characteristics and final pathological results were assessed retrospectively.
Results
86.3% of the patients are females ($n=120$) and 13.7% are males ($n=19$). The overall malignancy rate of FN cytology was 44.5% ($n=62$). There was no significant difference in NLR between the benign and malign groups (NLR= 2.12 ± 1.05 and 1.98 ± 0.92, respectively, $P=0.496$). When USG features were evaluated, hypoechogenicity and irregular margins was found associated with malignancy risk ($P=0.006$).
Conclusion
Our study showed no association between NLR and malignancy risk in thyroid nodules diagnosed as FN on cytology. The NLR is used as a readily available and inexpensive biomarker of inflammation. Many studies emphasised the increased NLR is associated with poor prognosis and adverse survival in various solid tumors including differentiated thyroid tumors. But we concluded NLR is not useful in predicting malignancy risk of thyroid nodules diagnosed as FN on cytology.

DOI: 10.1530/endoabs.37.EP887

EP888

Accuracy of fine-needle aspiration of the thyroid in a University Teaching Hospital

Mohamed Ahmed[1], Michael Jeffers[2], John Feeney[3], Pardeep Govender[3], Mark Sherlock[1] & James Gibney[1]
[1]Department of Endocrinology, The Adelaide and Meath Hospital Incorporating the National Children's Hospital (AMNCH), Tallaght, Dublin, Ireland; [2]Department of Histopathology, The Adelaide and Meath Hospital Incorporating the National Children's Hospital (AMNCH), Tallaght, Dublin, Ireland; [3]Department of Radiology, The Adelaide and Meath Hospital Incorporating the National Children's Hospital (AMNCH), Tallaght, Dublin, Ireland.

Background
Thyroid fine-needle aspiration (FNA) is a safe, valuable and cost effective procedure and is now regarded as the investigation of choice for preoperative assessment of thyroid nodules. The reported sensitivity of thyroid FNA varies from 65 to 98% and the specificity from 73 to 98%.
Aim
The aim of this study was to assess the accuracy of this procedure correlating cytology with histological outcomes, and to audit our practice against standard recommendations and published literature.
Methods
The cytological diagnoses of all thyroid FNA biopsies performed during the 5 years period (2008–2012) were retrieved retrospectively from the Pathology Laboratory Information System.
Results
567 thyroid FNAs were performed on 433 patients. The cytological diagnoses were as follows: Thy1 (non-diagnostic) in 63 (11.1%) cases, Thy2 (benign) in 424 (74.8%) cases, Thy3 (follicular lesion) in 54 (9.5%) cases, Thy4 (suspicious for malignancy) in nine (1.6%), and Thy5 (malignant) in 17 (3%) cases. Of 63 cases which were non-diagnostic, 25 had a repeat sampling, and of those a diagnostic aspirate was achieved in 84% ($n=21$) of cases. 80% of FNAs were performed under US guidance with onsite cytopathology evaluation, and the inadequacy rate was significantly lower in the US guided FNA compared to the free-hand aspirates (8.7% vs 15.7%, respectively, $P<0.05$). 111 patients had either partial or total

thyroidectomy, of which 69 (62.2%) were benign and 43 (37.8%) were malignant nodules. The sensitivity and specificity for detecting neoplasia were 87.5 and 83% respectively.
Conclusions
Thyroid FNA is a reliable and accurate procedure in triaging patients with thyroid nodule for surgery. Our findings are consistent with the standard recommendations and published literature. The use of US guided FNA coupled with onsite evaluation by pathologist should be the standard practice in all cases of thyroid nodules referred for FNA in order to reduce inadequacy rate and improve accuracy.

DOI: 10.1530/endoabs.37.EP888

EP889

Pleural metastasis of papillary thyroid carcinoma: case report and review of literature

Ahmed-Ali Leila, Fedala Nora Soumeya & Chentli Farida
Department of Endocrinology and Metabolic Disease, Bab El Oued Hospital, Algiers, Algeria.

Introduction
Papillary thyroid carcinoma (PTC) has generally good prognosis, and distant spread is rare. Common sites of distant metastasis are lung parenchyma and bone. Pleural metastasis is less common (0.6%), and most cases have been detected because of pleural effusion. Malignant pleural effusion is a poor prognostic factor among patients with PTC. We report a case of pleural metastasis of PTC proved by pleural biopsy.
Case report
A 62-year-old man was referred to our unit for pleural effusion and lung metastases which pleural biopsy showed the thyroid origin. He had undergone total thyroidectomy. Histopathological examination revealed a multifocal thyroid papillary carcinoma (PT3NXM2). Up-take scan after radioiodine therapy was positive in cervical and lungs. After pathological diagnosis, the serum thyroglobulin level was 6090 ng/ml. The rest of the staging (cerebro spinal MRI and bone scan) came back without abnormalities.
Conclusion
Pleural metastases of thyroid carcinomas are rare and usually occur in a context of metastatic spread. Their specific management is difficult because of the recurrent nature of the effusion. The median survival duration after pleural effusion development is reported to be <1 year, and most reported cases have had poor prognoses.

DOI: 10.1530/endoabs.37.EP889

EP890

Sentinel lymph node biopsy in medullary thyroid carcinoma: a pilot study

Radan Dzodic[1,2], Nada Santrac[2], Merima Oruci[2], Ivan Markovic[1,2], Igor Djurisic[2], Marko Buta[2] & Gordana Pupic[3]
[1]Medical School, University of Belgrade, Belgrade, Serbia; [2]Surgical Oncology Clinic, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia; [3]Department of Pathology, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia.

Introduction
Serum calcitonin levels (sCT) in medullary thyroid carcinoma (MTC) correlate with the tumour size and disease progression. Lymph node (LN) metastases can be verified even in sCT lower than 100 pg/ml. The extent of LN dissection has not yet been standardised. The aim of this pilot study was to show our experience with sentinel lymph node (SLN) biopsy of jugulo-carotid chain (JCC) in selection of patients with MTC for modified radical neck dissection (MRND).
Materials and methods
Following protocols of our institution, all patients with confirmed thyroid carcinoma on intraoperative frozen section analysis undergo total thyroidectomy, central neck dissection, and SLN biopsy of JCC. SLN biopsy is performed after peritumoral injection of 1%-methylene blue dye (0.2–0.5 ml), and frozen section examination follows, in order to make decision on further MRND. For this study, we have selected 13 patients treated surgically from year 2007 to 2015 due to suspect MTC with increase of sCT, clinically and ultrasonically verified thyroid tumour and 'clear' regional lymph nodes. Inclusion criteria for this pilot study were sCT lower than 1000 pg/ml and subcentimetre tumour size. All patients had uni- or bilateral SLN biopsy of supraomohyoid regions (II–III). Besides these blue stained SLNs, we have removed surrounding LNs of II and III region in order to obtain more precise definite pathological evaluation of LNs.
Results
In dissected central LNs, metastases were not verified. All SLNs were identified as benign, both on frozen section and definite pathological analysis, thus there were no false negative results. Besides SLNs, all LNs extirpated from II to III regions were benign on definite pathology reports. On postoperative check-ups, all sCT were in the normal range, patients suffered no complications of thyroid surgery and none have disease relapses. The SLN biopsy method's accuracy is 100%.
Conclusion
This pilot study is the first reported experience with SLN biopsy of JCC in MTC using methylene blue dye. SLN biopsy can be precisely used for intraoperative assessment of lateral neck compartment. It enables adequate surgery for patients with subcentimetre MTC and sCT under 1000 pg/ml, avoiding unnecessary prophylactic MRND.

DOI: 10.1530/endoabs.37.EP890

EP891

Papillary thyroid carcinoma in children: 33 years of experience of a single institution in Serbia

Marko Buta[1], Ivan Markovic[1,2], Milovan Matovic[3,4], Nada Santrac[1], Igor Djurisic[1], Zorka Milovanovic[5], Gordana Pupic[5] & Radan Dzodic[1,2]
[1]Surgical Oncology Clinic, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia; [2]Medical School, University of Belgrade, Belgrade, Serbia; [3]Department of Nuclear Medicine, Clinical Center of Kragujevac, Kragujevac, Serbia; [4]Medical School, University of Kragujevac, Kragujevac, Serbia; [5]Department of Pathology, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia.

Background
Well-differentiated thyroid carcinoma in children is rare but it shows aggressive behaviour. Gross lymph node metastases and distant metastases are common on first clinical presentation.
Patients and methods
During 33 years (1981–2014) at the Institute of Oncology and Radiology of Serbia 24 children were operated due to papillary thyroid carcinoma. Mean age was 12.6 (range 7–16) years. At the time of diagnosis 12.5% patients had lung metastases. Total thyroidectomy or completion of thyroidectomy was performed in all cases followed with central neck dissection and frozen section examination of the jugulo-carotid compartments. Median follow-up was 10.1 (range 2.0–29.4) years.
Results
pT1a tumours were found in 12.5%, pT1b in 25%, pT2 in 20.83%, pT3 in 25%, and pT4 in 16.67%. All patients had papillary thyroid carcinoma. Multifocal tumours were found in 79.17% and capsular invasion in 83.33%. Lymphonodal metastases in either central or lateral neck compartments were found in 75% of patients. Median DFI has not been reached and overall survival rate was 100%.
Conclusion
Papillary thyroid carcinoma in children is characterised with high rate of loco-regional aggressiveness, multifocality, capsular invasion, lymph node metastases, and distant metastases at the time of diagnosis. Extensive surgical approach should be performed in both primary and recurrent disease in young patients with well-differentiated thyroid carcinoma in order to achieve loco-regional disease control and long disease free survival.

DOI: 10.1530/endoabs.37.EP891

EP892

Lymphonodal metastases in incidental thyroid microcarcinomas verified by sentinel lymph node biopsy of jugulo-carotid chain

Merima Oruci[1], Ivan Markovic[1,2], Nada Santrac[1], Igor Djurisic[1], Marko Buta[1], Gordana Pupic[3], Dusica Gavrilovic[4] & Radan Dzodic[1,2]
[1]Surgical Oncology Clinic, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia; [2]Medical School, University of Belgrade, Belgrade, Serbia; [3]Department of Pathology, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia; [4]Institute for Oncology and Radiology of Serbia, Data Center, Belgrade, Serbia.

Introduction
The aim of this study was to determine frequency of lymphonodal metastases in jugulo-carotid chain (JCC) and central neck compartment in incidental thyroid

microcarcinomas (ITMC), as well as to examine whether sentinel lymph node (SLN) biopsy of JCC is an accurate technique to select patients with true positive, but clinically and ultrasonically negative lymph nodes, for modified radical neck dissection (MRND).
Materials and methods
Out of all patients operated in our Institution from 2004 to 2013 for multinodal goitre, Hashimoto's thyroiditis, adenomas, Graves' disease or increase of serum calcitonin concentration, for the purpose of this study, we have selected 117 who had ITMC and were surgically treated with total thyroidectomy (lobectomy in only one patient), sampling or complete dissection of central lymph nodes and SLN biopsy in JCC. As a standard procedure, SLN mapping was performed with 0.2 ml of 1% methylene blue dye injected just beneath thyroid gland capsule. SLNs were examined by frozen section and if positive, additional MRND was done. Hystopathological analysis showed 108 papillary, six medullary, and three combined papillary and medullary thyroid microcarcinomas <1 cm in diameter.
Results
Multicentric carcinomas were recorded in 39.32% of patients. In patients with lymphonodal metastases (24.79%), JCC metastases were found in 7.69% and central in 20.51%. Specificity and sensitivity of method are 100 and 57.14%, positive and negative predictive values are 100 and 97.3%. Method's accuracy is 97.39%.
Conclusion
Data showed high percentage of metastases in central neck compartment. SLN biopsy is a method more precise than clinical examination and ultrasonography in detection of ITMC lateral lymphonodal metastases in N0 patients. Using SLN biopsy for intraoperative assessment of lateral compartment one can avoid unnecessary MRND, as well as prevent under-treatment of patients with good prognosis. In addition, this method helps optimizing ablative radioiodine treatment.

DOI: 10.1530/endoabs.37.EP892

EP893

Thyroid cancer arises in 5% of patients referred from primary care to a high-resolution thyroid clinic

Isabel Mancha Doblas[1], Carmen Maria Cortes-Salazar[2], Jose Carlos Fernandez-Garcia[1] & Francisco Tinahones[1]
[1]Endocrinology Department, Virgen de la Victoria University Hospital, Malaga, Spain; [2]Badolatosa Primary Care Centre, Seville, Spain.

Objective
To evaluate the prevalence of thyroid cancer in patients with suspected thyroid nodule referred from primary care.
Methods
Retrospective cohort study which included patients with suspected thyroid nodule referred from primary care to a high-resolution thyroid nodule clinic. Demographic and clinical characteristics were collected, all patients underwent thyroid ultrasound and subsequently, a fine-needle aspiration (FNA) was performed if thyroid nodules were >1 cm of diameter of if there was evidence of risk factors for thyroid carcinoma (in accordance with American Thyroid Association guidelines).
Results
987 patients were included in this study. After performing thyroid ultrasound the presence of a thyroid nodule was detected in 79.5% of patients (785 nodules) with a mean nodule diameter of 2 ± 1.15 cm. FNA was performed in 585 nodules (74.5% of all nodules). 11.8% of all cytological samples had suspected malignancy and 2.1% were malignant. Referral for surgery was required in 23.2% of patients (mainly because of nodule size or suspected malignancy). Malignancy was confirmed in 5.6% of thyroid nodules.
Conclusions
The prevalence of thyroid cancer in this cohort of patients from primary care is 5.6%. Thus, approximately one out of 20 thyroid nodules referred from primary care to a high-resolution thyroid clinic is proven to be malignant.

DOI: 10.1530/endoabs.37.EP893

EP894

Miliary tuberculosis mimicking papillary thyroid cancer metastasis

Adem Gungor[1], Naile Gokkaya[1], Arzu Bilen[2] & Habib Bilen[1]
[1]Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology and Metabolism, University of Ataturk, Erzurum, Turkey; [2]Faculty of Medicine, Department of Internal Medicine, University of Ataturk, Erzurum, Turkey.

Introduction
Papillary thyroid carcinoma (PTC) is the most frequently occurring subtype of thyroid differentiated cancers. PTC frequently metastasizes to the cervical lymph node region and metastasis rate of approximately 20–90% is available when diagnosed. Distant metastasis are usually the lungs, bone and brain metastases. Furthermore rarely the adrenal gland, skeletal muscle, ovaries, submandibular gland, sphenoid sinuses, liver and pancreatic metastases can be occurred. PTC's lung metastases can manifest as nodular, local or generalized lymphadenopathy, pleural effusion and miliary multiple metastases. Miliary metastases are extremely rare.
Case
A 40-year-old man was referred to Department of Pulmonary Diseases for complaints of cough with expectoration, dispnea and chest pain. Chest x-ray revealed miliary pulmonary lesions which was confirmed on computed tomography (CT) analysis. Because of clinical suspicion of miliary tuberculosis, bronchoscopic biopsy was performed. The papillary thyroid cancer metastasis was diagnosed in histological examination. Since the histological diagnosis was PTC, we checked the thyroid gland. Ultrasound examination of thyroid gland showed 10×15 mm hypoechoic solid nodule with micro calcification. The diagnosis of PTC was verified with cytological examination *via* ultrasound guided thyroid fine needle aspiration. Because of these findings total thyroidectomy was performed. Microscopically, this nodule was diagnosed PTC (hurtle cell variant) with capsular and lenfovascular invasion. After treatment with iodine 131 was planned patient was discharged.
Conclusion
Although PTC is known relatively lingering disease, the early metastases can be occurred before When diagnosis of PTC is established. Metastatic PTC may appear radiograhpically as solitary or multiple nodules and rarely diffuse micronoduler and reticular. So because of these paterns while evaluating the miliary lesions of lung the metastases of PTC must be come to mind.

DOI: 10.1530/endoabs.37.EP894

EP895

Analysis of thyroid cancer mortality between 1975 and 2011 in Andalusia, Spain

Ana R Romero-Lluch[1,2], Elena Navarro-González[1,2], M Cruz Almaraz-Almaraz[2], Jorge Díaz-Alemán[2], M Ángeles Gálvez-Moreno[2], Inmaculada Gavilán-Villarejo[2], Tomás Martín-Hernández[2], Carolina Sánchez-Malo[2], Elena Torres-Vela[2] & Francisco Viciana-Fernández[3]
[1]Virgen del Rocio University Hospital, Seville, Spain; [2]Thyroid Cancer working group, Andalusia, Spain; [3]Institute of Statistics and Cartography, Andalusia, Spain.

Introduction
The incidence of thyroid cancer (TC) is low, but rising over time. Some studies point to a possible increase in mortality rate (MR) from this cancer in certain areas of Spain and Andalusia. Our purpose was to analyse the TC mortality in Andalusia and study how it has changed in the last years. We also analysed differences by age, sex, and geographic area.
Methods
All deaths from TC were collected between January 1, 1975 and December 1, 2011. These deaths were classified by age, sex, and province. Data were obtained from the mortality register of the Andalusian Statistics and Cartography Institute and from the Regional Ministry of Health. We calculated specific MR standardized by the direct and indirect method (standardized mortality ratio-SMR-) for all Andalusia and for each province.
Results
Between 1975 and 2011, 1199 TC deaths were registered in Andalusia (62.1% women). In these 37 years the MR has not changed significantly. The MR is higher in women (0.5–1 deaths/100 000 population-year) than in men (0.4–0.7 deaths/100 000 population-year); however, it has remained stable in both genders over time. Mortality increases exponentially with age, ranging MR from 0.02–0.1 deaths/100 000 population-year at 1930s up to 2–5 deaths/100 000 population per year at 1980s. Mortality is higher in men than in women up to 1940s, remains equal in both sexes between 1940s and 1970s and is higher in women over 1970s. There are small differences when comparing mortality in the Andalusian provinces. The SMR for whole Andalusia is 1. A SMR >1 indicates that there are more deaths observed than expected, as occurs in Seville, Granada, Cádiz and Huelva. Córdoba, Jaén, Almería and Málaga have a SMR <1.
Conclusions
Mortality from TC in Andalusia has remained stable over the last 37 years. There are differences in mortality in the Andalusian provinces. It is necessary to analyse the factors involved.

DOI: 10.1530/endoabs.37.EP895

EP896

Lymphocytic thyroiditis and differentiated thyroid cancer – challenges in follow-up

Diana Oliveira[1], Cristina Ribeiro[1], Maria João Martins[2], Sandra Paiva[1], Miguel Melo[1], Carolina Moreno[1], Daniela Guelho[1], Nuno Vicente[1], Luís Cardoso[1], Diana Martins[1] & Francisco Carrilho[1]
[1]Endocrinology, Diabetes and Metabolism Department, Coimbra Hospital and University Centre, Coimbra, Portugal; [2]Department of Pathology, Coimbra Hospital and University Centre, Coimbra, Portugal.

Introduction
Chronic lymphocytic thyroiditis (LT) is a very common condition, and its coexistence with papillary thyroid carcinoma has often been reported. Analytical and echographic challenges must be kept in mind in the follow-up of patients with both these disorders.
Case report:
We present the case of a woman with a history of multinodular goitre who underwent left thyroidectomy and isthmectomy at the age of 43, with the histopathological finding of papillary microcarcinoma associated with nodular hyperplasia and LT. Her follow-up included regular cervical and thyroid ultrasound and thyroglobulin (Tg) and antithyroglobulin autoantibodies (TgAbs) measurements. The remaining right thyroid lobe had a micronodular appearance on ultrasound; TSH was in the normal range; TgAbs were positive; Tg was undetectable. After 8 years of follow-up, ultrasound revealed a suspicious cervical lymph node. A fine-needle aspiration biopsy (FNAB) was performed, with the Tg concentration of FNAB washout liquid being 36 ng/ml and cytology revealing aspects of metastasis from papillary thyroid carcinoma. She underwent completion thyroidectomy and lymph node dissection. Histopathology revealed a 12 mm papillary carcinoma in the right thyroid lobe, with extension to perithyroidal adipose tissue. The patient was subsequently admitted for radioiodine remnant ablation.
Conclusions
In patients with thyroid papillary microcarcinoma who have had only partial thyroidectomy and are positive for TgAbs, neither Tg nor TgAbs can be used reliably; regular careful ultrasound evaluation is essential in the follow-up of these patients. On the other hand, due to known alterations in thyroid gland structure, LT may cause diagnostic performance of thyroid ultrasound to be inferior in detecting suspicious nodules. This case report brings attention to the different difficulties found in the follow-up of patients with coexisting LT and thyroid papillary carcinoma.

DOI: 10.1530/endoabs.37.EP896

EP897

RET M918T-exon 16 mutation in subjects with sporadic medullary thyroid cancer (sMTC)

Darko Katalinic[1], Miljenko Solter[2] & Nora Nikolac[2]
[1]University Hospital Centre Zagreb, Zagreb, Croatia; [2]University Hospital Centre Sisters of Charity, Zagreb, Croatia.

Medullary thyroid cancer (MTC) is a form of thyroid carcinoma which originates from the calcitonin-secreting neuroendocrine parafollicular cells of the thyroid. It accounts for 5–10% of all thyroid cancers, and it mostly occurs as a sporadic entity (sMTC), but a familial pattern is also possible. Somatic mutations of RET are reported in 20–80% of sMTCs. The majority of MTCs harbour a RET M918T-exon 16 mutation. In sporadic MTCs the RET gene is mutated in codon 918, where a methionine is substituted to a threonine. This transformation of RET gene promotes uncontrolled cell proliferation and tumoural development. The objective of this study was to assess the occurrence of MTC and co-occurring RET M918T mutation in the sample of Croatian population. A nonisotopic polymerase chain reaction (PCR) based single strand conformation polymorphism analysis and heteroduplex gel electrophoresis method was used to screen DNA extracted from 34 formaldehyde fixed and paraffin embedded sMTC specimens of the patients for M918T mutation in RET exon 16. Results were compared with the disease phenotype and clinical findings. A germline methionine/threonine point mutation at codon 918 of the RET tyrosine kinase domain was identified in 21 patients (61.7%) (16 females (76.1%) and five males (23.8%), aged 62–78 years). The first data about RET M918T mutational status in the sample of Croatian population with MTC shows that the incidence of RET exon 16 mutation is within generally valid limits. However, all subjects with RET M918T mutation had more aggressive phenotype and worse cancer-specific survival. These data should be confirmed on a larger study group in prospective studies in order to determine whether RET M918T mutation contribute to progression of sMTC. All obtained results could serve in selection of patients for RET-inhibitors therapy with vandetanib and cabozantinib and as predictive biomarkers the same therapy.

DOI: 10.1530/endoabs.37.EP897

EP898

Cytological variants of papillary thyroid carcinoma: clinical presentations according with the presence of BRAF mutation

Amelia Oleaga[1], Eider Etxeberría[1], Laura Calles[1], Fernando Goñi[1], Elena Fuertes[2], Maite Pérez de Ciriza[1], Aitziber Ugalde[2] & Miguel Paja[1]
[1]Endocrinology Department, Universitary Basurto Hospital, Bilbao, Spain; [2]Pathology Department, Universitary Basurto Hospital, Bilbao, Spain.

Introduction
BRAF(V600E) mutation has received great attention to improve risk stratification in patients with PTC. Its prognostic value in the different Cytological variants (CytV) of PTC is not well established. The aim of this study was to investigate differences in clinicopathological features according to CytV, among patients harbouring the mutation.
Methods
We evaluated 102 patients with pathological diagnosis of PTC. All of them underwent total thyroidectomy and radioiodine ablation, 87 central lymph node (LN) dissection (67 prophylactic, and 18 lateral neck dissection as well. DNA was extracted from neoplastic cells and BRAF mutation was detected by PCR and sequencing. Analysis included histological subtype, age, multifocality (MF), extrathyroidal extension (EET), LN metastases (LNMx), LNratio (LNR) (number of positive LN divided by the total amount of dissected nodes) and clinical remission(CR) after 1 year of initial treatment (stimulated thyroglobulin (Tg) undetectable, no presence of Tg antibodies and negative cervical ultrasound).
Results
patients harboured BRAF mutation (45,1%). According to CytV: 27/38 (71%) classic variant (CV), 3/33 (9%) follicular variant (FV) and 16/25 (64%) mixed forms (MV). In mutation carriers mean age was 47 years in CV, 58 in FV and 60 in MV. MF was present in 59% of CV, 66% FV, 50% MV. EET was found in 51% of CV, 33% FV, 33% MV. The rate of central LNMx was 85% in CV, 37%MV and no patients in FV. The LNR was 22.4% in CV, and 6.1% in MV. CR was achieved in 15 out of 20 evaluated patients with CV and all the 11 with MV.
Conclusions
In our series BRAF mutation is more prevalent in CV of PTC as it has been described previously, and at a younger age. We also emphasise the high prevalence of LNMx and the higher LNR found in patients with CV tumours. Given the prognostic value of BRAF mutation, these results confirm the more benign behaviour of FVPTC.

DOI: 10.1530/endoabs.37.EP898

EP899

Incidence and peculiarities of thyroid cancer in patients with type 2 diabetes mellitus

Tetyana Yuzvenko & Volodymyr Pankiv
Ukrainian Scientific and Practical Center of Endocrine Surgery, Transplantation of Endocrine Organs and Tissues of the Ministry of Health of Ukraine, Kiev, Ukraine.

Diabetes mellitus is a risk factor for cancer, specifically of breast, endometrium, bladder, liver, colorectum, and pancreas. The pathophysiology of how diabetes contributes to cancer growth or development is an area of active investigation. The aims is to study the frequency and morphological features of thyroid cancer in patients with type 2 diabetes mellitus (DM).
Materials and methods
The study involved 45 patients with thyroid cancer and type 2 DM. 980 patients with thyroid cancer who underwent treatment at the surgical department of the Ukrainian Scientific and Practical Center of Endocrine Surgery for the period from 2010 to 2012 years. The examination included the study of patients' complaints, measurement of blood glucose profiles, glycated hemoglobin, immunoreactive insulin (IRI), C-peptide, HOMA-IR index, lipid profile, ultrasound of thyroid and abdominal organs. In addition conducted fine needle aspiration of thyroid nodules before surgery, pathological examination after surgical treatment, the determination of interleukin-6 (IL-6). We studied the incidence of thyroid cancer in the general population of Ukraine. Statistical data were processed using Microsoft Excel. Results are expressed as the mean $\pm$ standard error indicators ($M \pm m$).
Results
The mean age of patients with type 2 DM and thyroid cancer was 59.2 ± 2.7 years, duration of DM (from the time of diagnosis) – 7.1 ± 1.3 years, body mass index (BMI) – 31.7 ± 2.6 kg/m^2. All patients established insulin resistance (IRI level was 31.26 ± 2.81 μ/l, HOMA-IR index – 14.57 ± 2.31). The frequency of type 2 DM among all patients treated with thyroid cancer is 4.6%. Among patients with thyroid cancer and type 2 DM were mostly women (32; 71.1%). Most patients had papillary thyroid cancer (37; 82.2%) than follicular one. Among the total

population of Ukraine thyroid cancer had been diagnosed in 39 042 patients, representing 74.8 per 100 000. At the same time among the inhabitants of Kiev incidence of thyroid cancer reaches 3039 (177.5 per 100 000). Obviously that the presence of DM is associated with an increased risk development of thyroid cancer. The number of newly diagnosed patients with thyroid cancer in Ukraine increase and in 2011 was 2984, or 6.5 per 100 000 of population, but in some regions, for example, in Kiev and the Kiev region, the incidence is respectively 12.9 and 12.2 per 100 000 of population.

Conclusion

Patients with DM have a higher incidence of thyroid cancer compared with the general population. The frequency of type 2 DM among patients with thyroid cancer is 4.6% with a predominance of women (71.1%). Most patients had the papillary thyroid cancer (82.2%) than follicular one.

DOI: 10.1530/endoabs.37.EP899

EP900

Concomitant thyroid nodules in primary hyperparathyroidism

Mustafa Sahin, Gozde Sengul aycicek, Demet corapcioglu, Rifat emral, Sevim gullu, Murat Faik erdogan, Vedia Tonyukuk Gedik, Nilgun Baskal & Ali Riza Uysal
Ankara University, Ankara, Turkey.

Objectives

Coexisting thyroid nodules affect the treatment choice for PHPT. We aimed to evaluate the incidence of concomitant thyroid nodules in patients with primary hyperparathyroidism and to investigate the relationship between thyroid nodule volume, thyroid gland volume and thyroid nodules with clinical and laboratory parameters.

Materials and methods

This study was carried out at Ankara University Endocrinology and Metabolism Department. 183 patients with biochemically confirmed primary hyperparathyroidism and 30 patients with no any other co morbidities, as a control group, were evaluated. USG images, FNAB results, clinic and laboratory parameters of patients were reviewed from medical data.

Results

Thyroid nodules were higher in the PHPT patients ($P<0.001$). Six of the patients had papillary thyroid carcinoma and one had follicular neoplasia. Patients with thyroid nodules had higher 25-OH vitamin D levels ($P=0.026$). Thyroid volume was positively correlated with BMI ($P=0.001$ $r=0.272$), fasting glucose ($P=0.22$ $r=0.173$) and negatively correlated with TSH ($P=0.01$ $r=-0.194$). Number of nodules and nodule volume were positively correlated with creatinine ($P=0.036$ $r=0.158$) and negatively with GFR ($P=0.018$ $r=-0.179$). Also nodule volume was positively correlated with 25-OH vitamin D level ($P=0.04$ $r=0.154$). In regression analyses thyroid volume was found to be in relation with creatinine, HDL, 24 h urinary calcium and phosphorus; number of nodules with age, creatinine, GFR, BMI, HDL, 25-OH vitamin D, albumin and 24 h urinary calcium. The patients with malignancy had higher T4 lower TSH and better lumbar *T*-scores. But we couldn't find any relationship between 25-OH D levels, glucose levels and malignancy.

Conclusion

Thyroid nodules are more common in patients with primary hyperparathyroidism compared to normal group and considerable number of patients with nodules has thyroid cancer. Decreased GFR seems to be related with this increased incidence. Preoperative evaluation of thyroid gland with USG prevents missing thyroid disease especially a malignancy and unnecessary re-operative surgery.

DOI: 10.1530/endoabs.37.EP900

EP901

Differentiated thyroid carcinoma in geriatric patients: a single centre experience with 7 years of follow-up

Mesut Ozkaya[1], Umut Elboga[2], Ayten Eraydın[1] & Y Zeki Celen[2]
[1]Department of Endocrinology, Gaziantep University, Gaziantep, Turkey; [2]Department of Nuclear Medicine, Gaziantep University, Gaziantep, Turkey.

Introduction

We evaluated the characteristics of differentiated thyroid carcinoma in geriatric patients and factors that influenced long-term survival in this retrospective study design. Among 1188 patients with differentiated thyroid carcinoma who were treated at our institution over the past 7 years, 144 patients were identified who were age 65 years or older(age range:65–88 years) at the time of their initial diagnosis. This study conducted a retrospective analysis of the patients and factors that influenced long-term survival of these 144 patients, who had a median follow-up of 5.5 years (range, 2–7 years).

Results

There were 105 female patients and 39 male patients (female to male ratio, 2.6:1). 86 tumours were papillary, 48 tumours were follicular, and ten tumours were Hurthle cell carcinoma. One hundred 11 (77%) of patients presented with a thyroid mass, and 104 (72.9%) of tumours pathologic stage were T3 or T4. Lymph node disease was evident at presentation in 66 (45.8%) of patients, and distant metastases were documented at diagnosis in 35 (24.3%) of patients. 122 (84.7%) patients underwent total thyroidectomy, and the remaining patients underwent biopsy only. Radioiodine was administered to 108 (75%) patients. The specific survival rates were 93, 90, and 86% at 2, 5, and 7 years follow up respectively. Multivariate analysis showed that the presence of metastases was the most important independent prognostic factor for survival. Survival was greatest in patients with tumours <1 cm in diameter, characterized by the absence of extraglandular spread and lymph node.

Conclusion

Differentiated thyroid carcinoma appears more aggressive in geriatric patients. A large proportion of tumors showed extrathyroid spread and distant metastases. This may justify a more aggressive surgical strategy with possible prophylactic lymphadenectomy, in addition to ablative therapy with iodine and suppressive therapy with levothyroxine.

DOI: 10.1530/endoabs.37.EP901

EP902

Evodiamine inhibits human thyroid cancer cells *in vitro* and *in vivo*

Ying-Ray Lee[1], Chieh-Hsiang Lu[2], Yi-Sheng Chang[1], Shu-Hsin Chen[1] & Yi-Wen Liu[3]
[1]Translational Medicine Center, Chiayi Christian Hospital, Chiayi City, Taiwan; [2]Division of Endocrinology and Metabolism, Department of Internal Medicine, Chiayi Christian Hospital, Chiayi City, Taiwan; [3]Department of Microbiology, Immunology and Biopharmaceuticals, College of Life Sciences, National Chiayi University, Chiayi City, Taiwan.

Thyroid cancer is the most prevalent cancer among endocrine malignancies. In clinically, surgical resection combined with radioactive iodine therapy has been proved effective in treating differentiated thyroid cancer, including papillary and follicular thyroid cancers (FTC). However, patients with incurable differentiated thyroid cancer (DTC), poorly differentiated thyroid cancer (PDTC) and anaplastic thyroid cancer (ATC) exhibit worse prognosis. Therefore, a novel and effective treatment is urgently needed to deal with the current treatment. Evodiamine is one of the important components isolated from Chinese herb Wu-Chu-Yu, and has been demonstrated to contribute on anti-inflammatory effects, anti-angiogenesis, anti-tumor growth, anti-invasive and metastatic activities, and up-regulating apoptosis. In the present study, we examined the effects of evodiamine in FTC, PDTC and ATC cells, respectively. Evodiamine inhibited cellular proliferation and the colonies formation of FTC, PDTC and ATC cells. Cell cycle arrest at G2/M phase was found in all of the cells during evodiamine treatment. Moreover, caspase-dependent apoptosis in these cells was also revealed under evodiamine treatment. In addition, autophagy induction was also found in evodiamine treated human thyroid cancer cells. Finally, we verified the effects of evodiamine on anti-human thyroid cancers in a xenograft nude mice model. Our results demonstrate that evodiamine induces cell cycle arrest, caspase-dependent apoptosis and autophagy leading to inhibit proliferation of multiple types of human thyroid cancer cells. We suggest that evodiamine could be a chemo-therapeutic candidate for human thyroid cancers.

Disclosure

This study was supported by the research grant from Ministry of Science and Technology of the Republic of China (NSC 101-2314-B-705-003-MY3).

DOI: 10.1530/endoabs.37.EP902

EP903

Familial non-medullary thyroid cancers tend to be more bilateral and have more capsular invasion compared to non-familial ones

Dilek Yazici[1], Yersu Kapran[2], Onur Demirkol[3], Tarik Terzioglu[4], Serdar Tezelman[5] & Faruk Alagol[1]
[1]Section of Endocrinology and Metabolism, Koç University Medical School, Istanbul, Turkey; [2]Department of Pathology, American Hospital, Istanbul, Turkey; [3]Department of Nuclear Medicine, Koç University Medical School, Istanbul, Turkey; [4]Department of General Surgery, American Hospital, Istanbul, Turkey; [5]Department of General Surgery, Koç University Medical School, Istanbul, Turkey.

Introduction
Currently, about 5–15% of non-medullary thyroid cancers (FNMTC) are considered to be of familial origin. These are either syndrome-associated tumours or non-syndromic tumours. The aim of the study was to determine the clinical, pathological and biochemical characteristics of FNMTC compared to non-familial ones with a follow-up of 10 years.
Methods
Among FNMCT followed by a single physician, 62 patients with papillary cancer were screened retrospectively.
Results
(40.3%) patients had either one or more of their first-degree relatives with papillary cancer. Age (48.1 ± 15.1 years vs 45.3 ± 13.1 years), female/male ratios (20/5 vs 29/8) and age at diagnosis (44.1 ± 12.1 yrs vs 39.4 ± 10.9 years) were similar. Bilateral tumours (7/25 vs 5/32, $P=0.01$) and capsular invasion (11/25 vs 9/28, $P=0.004$) were more frequent in FNMTC compared to non-familial ones. Maximum tumour diameter (0.9 ± 0.6 cm vs 1.3 ± 1.0 cm) was comparable. Multicentricity (8/25 vs 8/37), lymph node metastasis (5/25 vs 6/37), vascular invasion (5/25 vs 5/37 patients), number of patients being operated more than once (4/25 vs 8/37 patients), having radioiodine therapy (10/25 vs 13/37), having classical tumour subtypes (11/25 vs 15/37) were comparable among groups. Postoperative thyroglobulin (0.48 ± 1.02 vs 0.65 ± 1.48) and TSH levels (0.16 ± 0.26 vs 0.25 ± 0.45) at 1st and (0.31 ± 0.44 vs 0.44 ± 0.76 thyroglobulin and 0.02 ± 0.03 vs 0.32 ± 0.69 TSH) 5th year follow-up were comparable. When patients with two cases ($n=20$) and more than two cases in family ($n=5$) were compared, all above mentioned parameters were similar among groups.
Conclusion
In conclusion, FNMTC tends to be more bilateral and has a higher rate of capsular invasion compared to non-familial ones.

DOI: 10.1530/endoabs.37.EP903

EP904

Adjuvant radioiodine (RAI) treatment reduces the risk of relapse in low advanced differentiated thyroid carcinoma (DTC)

Jolanta Krajewska, Michal Jarzab, Agnieszka Czarniecka, Aleksandra Kukulska, Daria Handkiewicz-Junak, Zbigniew Wygoda, Zbigniew Puch, Ewa Paliczka-Cieslik, Jozef Roskosz & Barbara Jarzab
M.Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland.

The routine use of adjuvant RAI treatment in low-risk DTC remains controversial due to the lack of unequivocal evidences of its effectiveness in radically operated subjects. The aim of the study was a retrospective evaluation of long-term outcomes of combined DTC treatment to evaluate the impact of adjuvant RAI therapy in the low risk group. Primary hypothesis was: 'if adjuvant RAI treatment was unnecessary, a delay in RAI administration would have no impact on long-term outcomes'.
Material and methods
The study group consisted of 510 DTC patients, staged pT1b-T4N0-N1M0. Total thyroidectomy was carried in all subjects and followed by RAI therapy. On the basis of initial DTC stage and postoperative stimulated serum thyroglobulin (Tg) level 272 patients were classified as a low risk group (T1–T3, N0Nx and Tg $<$ 10 ng/ml), 90 as high risk (stimulated Tg >30 ng/ml), whereas 148 remaining constituted an intermediate risk group. Median follow-up was 12.1 years (range 1.5–15.2).
Results
To properly assess the efficacy of adjuvant RAI therapy all groups were divided depending on time of RAI administration. Next, subjects treated with RAI up 9 months after DTC diagnosis were compared to subgroups treated later: within 9–24 and >24 months. In the low risk group, patients treated with RAI up to 9 months, showed no recurrences, whereas among those, treated 9–24 months and >24 months after diagnosis, the risk of recurrence were 5.5 and 7.1%, respectively ($P=0.035$). There was no significant time depending difference in both intermediate and high risk groups.
Conclusion
Adjuvant RAI therapy, administered within a short time period after the operation significantly reduces the risk of cancer recurrence in the low advanced DTC. We believe that the exclusion of low risk patients from RAI therapy, suggested by the ATA and European guidelines, is not justified.

DOI: 10.1530/endoabs.37.EP904

EP905

Efficacy and safety of an outpatient low radioide dose for remnant thyroid ablation in low risk papillary thyroid carcinoma (PTC)

Gabriel Obiols, Amparo García-Burillo, Carles Zafon, Joan Castell & Jordi Mesa
Hospital Vall d'Hebron, Barcelona, Spain.

In PTC, radioiodine required dose for thyroid remnant ablation is uncertain. Recent works show that low doses may be sufficient for low risk patients.
Aim
To evaluate the efficacy and safety of thyroid remnant ablation in patients with low-risk PTC by using 1100 MBq (30 mCi) outpatient doses.
Materials and methods
Twenty-five patients (24 women, 55 years-old mean age, range 34–77) referred for ablation of postsurgical thyroid remnants diagnosed with low-risk PTC (pT1-T2, N0, M0) were studied. After total thyroidectomy, an outpatient ablation was performed with 1100 MBq of ^{131}I under rhTSH stimulation with strict radiation protection measurements and dosimetry control at home environment. Whole body scan (WBS) and SPECT-CT were performed on the fifth day. Control of therapeutic efficacy was performed at 6 months, using WBS and SPECT-CT with ^{123}I after stimulation with rhTSH. Basal and post-stimulated thyroglobulin levels were determined in both studies. Ablation was considered successful when no abnormal activity was observed in WBS and SPECT-CTs and when basal/stimulated thyroglobulin levels were under 1 and 2 ng/ml, respectively.
Results
All 25 patients showed thyroid uptake without uptaking adenopathies in the WBS and SPECT-CTs performed on the fifth day after administration of ^{131}I. In 23/25 patients (92%) a successful ablation at 6-month efficacy control was achieved. One patient (5.1 ng/ml stimulated Tg) was re-treated with a new dose of 30 mCi and a second patient (2.3 ng/ml stimulated Tg) spontaneously normalised her basal and stimulated Tg levels at the 18-month control. Dosimetry on family members showed exposure levels of <0.2 mSv.
Conclusion
The postsurgical outpatient treatment with an activity of 1100 MBq is safe for the family environment and cost-effective in a great majority of patients with low-risk PTC.

DOI: 10.1530/endoabs.37.EP905

EP906

Wide screening of RET proto-oncogene in Iranian medullary thyroid carcinoma patients: 13 years study

Mehdi Hedayati[1], Marjan Zarif Yeganeh[1], Sara Sheikholeslami[1] & Fereidoun Azizi[2]
[1]Research Institute for Endocrine Sciences, Cellular and Molecular Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [2]Research Institute for Endocrine Sciences, Endocrine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Introduction
Thyroid cancer is the most common endocrine cancer and medullary thyroid carcinoma (MTC) is one of the most malignant thyroid tumours which occur in both hereditary (25%) and sporadic (75%) forms. Mutations of the RET proto-oncogene in MTC development have been well demonstrated. The aim of the study was to investigate the mutational spectrum of exons 3, 5, 8, and 10–18 of RET proto-oncogene in MTC patients.

Material and methods
This retrospective study has been started since 2001 in Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, and Tehran, Iran. 399 participants, including 233 patients (176 sMTC, 40 FMTC, eight MEN2A, four MEN2B, five pheochromocitoma), and 166 relatives were evaluated. Genomic DNA was extracted by the standard Salting Out/ProteinaseK method and Mutation detection was performed through direct DNA sequencing. Sequence analysis was performed by Chromas Software version 2.3.
Results
Totally, in 233 patients (131 female, 102 male) and 166 relatives (91 female, 75 male), 82 mutations were identified in RET main exons, including 10, 11, and 13–16. Furthermore, 282 single nucleotide polymorphism (SNP) were found in exons 3, 13, and 14. Interestingly, G691S SNP and S904S SNP were 100% in linkage disequilibrium in 131 patients and 87 relatives. The most common mutation in our population were C634Y and C634R (4%) whereas C618R, C618S, C620G, L887L mutations had rare allele frequency (0.3%). Moreover, R886Q mutation was detected in exon 15 in two members of a family affected with MTC for the first time.
Discussion
Exon 11 and after that exon 10 were the most frequently mutated exons of *RET* proto-oncogene in MTC patients in Iranian population. As about half of patients with the hot spot mutations had the G691S/S904S haplotype simultaneously, further analysis needs for clarifying the effect of multiple risk alleles in MTC development.

DOI: 10.1530/endoabs.37.EP906

EP907

Wide screening of RET proto-oncogene in Iranian medullary thyroid carcinoma patients: 13 years study

Mehdi Hedayati[1], Marjan Zarif Yeganeh[1], Sara Sheikholeslami[1] & Fereidoun Azizi[2]
[1]Research Institute for Endocrine Sciences, Cellular and Molecular Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [2]Research Institute for Endocrine Sciences, Endocrine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Introduction
Thyroid cancer is the most common endocrine cancer and medullary thyroid carcinoma (MTC) is one of the most malignant thyroid tumours which occur in both hereditary (25%) and sporadic (75%) forms. Mutations of the RET proto-oncogene in MTC development have been well demonstrated. The aim of the study was to investigate the mutational spectrum of exons 3, 5, 8, and 10–18 of RET proto-oncogene in MTC patients.
Material and methods
This retrospective study has been started since 2001 in Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, and Tehran, Iran. 399 participants, including 233 patients (176 sMTC, 40 FMTC, eight MEN2A, four MEN2B, five pheochromocitoma), and 166 relatives were evaluated. Genomic DNA was extracted by the standard Salting Out/ProteinaseK method and Mutation detection was performed through direct DNA sequencing. Sequence analysis was performed by Chromas Software version 2.3.
Results
Totally, in 233 patients (131 female, 102 male) and 166 relatives (91 female, 75 male), 82 mutations were identified in RET main exons, including 10, 11, and 13–16. Furthermore, 282 single nucleotide polymorphism (SNP) were found in exons 3, 13, and 14. Interestingly, G691S SNP and S904S SNP were 100% in linkage disequilibrium in 131 patients and 87 relatives. The most common mutation in our population were C634Y and C634R (4%) whereas C618R, C618S, C620G, L887L mutations had rare allele frequency (0.3%). Moreover, R886Q mutation was detected in exon 15 in two members of a family affected with MTC for the first time.
Discussion
Exon 11 and after that exon 10 were the most frequently mutated exons of RET proto-oncogene in MTC patients in Iranian population. As about half of patients with the hot spot mutations had the G691S/S904S haplotype simultaneously, further analysis needs for clarifying the effect of multiple risk alleles in MTC development.

DOI: 10.1530/endoabs.37.EP907

EP908

Ratio of lymph node aspiration washout thyroglobulin levels to whole blood and serum washout thyroglobulin levels in patients with differentiated thyroid carcinoma: a new approach for standardisation of measurements and increased accuracy

Cevdet Aydin[1], Didem Ozdemir[1], Muhammed Sacikara[1], Sefika Burcak Polat[2], Aylin Kilic Yazgan[3], Seyda Turkolmez[4], Eda Demir Onal[2], Reyhan Ersoy[1] & Bekir Cakir[1]
[1]Department of Endocrinology and Metabolism, School of Medicine, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey; [2]Department of Endocrinology and Metabolism, Ataturk Education and Research Hospital, Ankara, Turkey; [3]Department of Pathology, School of Medicine, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey; [4]Department of Nuclear Medicine, School of Medicine, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey.

Introduction
High values of fine needle aspiration washout thyroglobulin (FNA-Tg) are diagnostic for metastatic lesions of thyroid cancer. However, there is not a consensus on cut-off for high Tg level. The most important confounding factor for FNA-Tg is inability to calculate Tg per unit volume because residual aspiration material in the needle cannot be known exactly. Another problem is possible contamination of whole blood during lymph node aspiration. In this study, we aimed to determine a more accurate and standardised parameter for FNA-Tg.
Methods
Ultrasonographically suspicious 155 lymph nodes in 120 patients with histopathologically confirmed differentiated thyroid cancer and suspicious for malignancy/malignant thyroid nodule FNA result in cytology were evaluated. Tg was measured in samples obtained by aspiration (FNA) and non-aspiration (FNNA) biopsy. The highest value obtained by these methods from the same lymph node was defined as FNB-Tg. Simultaneous venous blood sample was taken. Tg was measured from whole blood and serum washouts which were obtained by using syringes and needles identical to ones used for lymph node biopsy.
Results
Data of 16 lesions in 14 patients who underwent lymp node dissection were analysed. FNNA-Tg, FNB-Tg/whole blood washout-Tg, FNB-Tg/serum washout-Tg, FNB-Tg/serum Tg were significantly higher in malignant lymph nodes compared to benign ones. Areas under the ROC curve for FNNA-Tg, FNNA-Tg/whole blood washout-Tg, FNNA-Tg/serum washout-Tg were statistically significant for the discrimination of benign and malignant lymph nodes. Best cut-off values for FNNA-Tg and FNB-Tg were 15.86 and 31.8 ng/ml. respectively. Among ratios, best cut off values to discriminate benign and malignant lymph nodes were 5.44 for FNB-Tg/whole blood washout-Tg and 3.95 for FNB-Tg/serum washout-Tg.
Conclusion
Determining ratio of FNB-Tg to whole blood washout-Tg and/or serum washout-Tg might be a promising method for increasing accuracy and providing standardization of lymph node aspiration to detect malignant lymph nodes.

DOI: 10.1530/endoabs.37.EP908

EP909

The risk of thyroid cancer (TC) in a thyroid nodule on the basis of a tertiary reference TC center experience

Aleksandra Blewaska[1], Aleksandra Sygula[1], Ewa Chmielik[2], Ewa Stobiecka[2], Ewa Zembala-Nozynska[2], Agnieszka Czarniecka[3], Aleksander Sacher[3], Jolanta Krajewska[1], Aleksandra Kukulska[1] & Barbara Jarzab[1]
[1]Nuclear Medicine and Endocrine Oncology Department, M.Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland; [2]Tumor Pathology Department, M.Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland; [3]The Oncologic and Reconstructive Surgery Clinic, M.Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland.

A global TC risk in a single thyroid nodule is rather small and ranges between 1 and 11%. However, taking into consideration Bethesda System for Reporting Thyroid Cytopathology TC risk varies between distinct categories: 0–3, 5–15, 15–30, 60–75 and 97–99% for Bethesda class II–VI, respectively. However, these values may differ in a centre, specialized in TC. Therefore, the aim of this study was to evaluate the TC risk in patients referred to a tertiary reference TC centre.

Material
282 thyroid nodules were involved into a retrospective analysis. Fine needle aspiration biopsy (FNAB) was performed in all cases and followed by surgery regardless of the results of FNAB. Next, histopathological findings were compared with FNAB results.
Results
According to FNAB 26.9% thyroid nodules were classified as benign (Bethesda II), 28.7% as malignant (Bethesda VI), while 23.8% as indeterminate (Bethesda III + IV + V). Among indeterminate nodules 3/67 were diagnosed as Bethesda III, 23/67 as follicular neoplasm (Bethesda IV), whereas 41/67 were suspicious for malignancy (Bethesda V). For 20.6% remaining tumours the FNAB result was nondiagnostic (Bethesda I). TC was diagnosed by histopathological examination in 171 tumours (60.6%), among them in 21/76, 39/67, 81/81 and 30/58 preoperatively classified as benign indeterminate, malignant and nondiagnostic, respectively. 96 nodules were benign in histopathology, while for 15 others no data were available. Finally, the risk of TC evaluated on the basis of aforementioned data was 27.6% for benign nodules, 39.1% for follicular neoplasm, 70.7% for nodules suspicious for malignancy and 100% when tumour were classified as malignant. Surprisingly, TC was confirmed after surgery in 51.7% with nondiagnostic FNAB.
Conclusions
The risk of TC in thyroid nodules referred to specialised thyroid cancer center is substantially higher than in routine practice. Thus, more careful procedures, including molecular markers are necessary to state a proper diagnosis and start the treatment on time.

DOI: 10.1530/endoabs.37.EP909

EP910

Thyroid cancer in Ireland: a 10-year review of the National Cancer Registry

Paul Lennon[1], Sandra Deedy[2], Marie-Louise Healy[1], John Kinsella[1], Conrad Timon[1] & James Paul O'Neill[3]
[1]St James's Hospital, Dublin, Ireland; [2]National Cancer Registry Ireland, Cork, Ireland; [3]Royal College of Surgeons, Ireland, Dublin, Ireland.

Introduction
The increased incidence of thyroid cancer is driven mainly by a large increase in papillary thyroid cancer (PTC). The number of patients that succumb to the disease has remained stable. The aim of our study is to analyze the incidence and mortality of thyroid cancer in Ireland.
Methods and design
A retrospective analysis of the National Cancer Registry was undertaken, between 1st of January 1998 and the 31st December 2007. The Kaplan–Meier method was used to determine overall survival using Stata 13 software.
Results
A total of 949 patients were diagnosed, 781 (82.2%) were well-differentiated thyroid cancers (papillary 565, follicular 177, Hurtle cell 39) whilst there were 44 medullary thyroid cancers and 61 anaplastic thyroid cancers. The female to male ratio was 3:1, with a median overall age of 47. This was significantly lower in women at 45, then men at 52 ($P = 0.0000$). The incidence of thyroid cancer increased from 1.43/100 000 to 3.61/100 000. This increase was in the mainly attributed to PTC, rising from 0.63 to 2.46/100 000. The number of deaths from the disease remained stable at 0.63–0.59/100 000. There was no survival difference between those under going total thyroidectomy vs thyroid lobectomy for PTC (hazard ratio 0.868, 95% CI 0.598–1.26, $P = 0.457$).
Conclusions
These results correlate with studies that demonstrate that although an increase in incidence of thyroid has been found, the number of patients dying from the disease has remained stable. This emphasises the need for a new treatment paradigm of risk stratification in order to ensure maximum benefit for the patient.

DOI: 10.1530/endoabs.37.EP910

EP911

Fine needle aspiration cytology, do cytology technicians make the difference?

Ricardo Capitao, Catarina Moniz, Catarina Sararaiva, Rute Ferreira, Clotilde Limbert, Marlene Carriço, Maria Carvalho, Claudia Linares, Diamantina Branco, Sancia Ramos, Isa Martins, Jose Duraes & Carlos Vasconcelos
Centro Hospitalar Lisboa Ocidental, Lisbon, Portugal.

Introduction
The fine needle aspiration cytology (FNAC) of thyroid nodules is the procedure of choice in the diagnostic approach of nodular thyroid disease. Despite showing a sensitivity of 83% and a specificity of 92%, many of the results are non-diagnostic. One of the factors that can contribute to this number is the proper procedure of the smear.
Objective
To compare the FNAC's results in our team with and without the contribution of an expert Cytology Technician (CT).
Methods
All FNACs results (based on Bethesda classification) were registered in the period of 2 consecutive years in our hospital. The results were distributed between two groups: – Group A: 01/01/2013 to 31/12/2013 without CT support. Group B: 01/01/2014 to 31/12/2014 with CT support.
Results
The total of FNACs obtained was 3107 (1538 in Group A and 1569 in Group B). Benign lesions were the most frequent diagnosis in both groups. A statistical relationship between the presence of a CT and the Bethesda classification in the evaluation of FNACs was obtained (χ^2 test, $P < 0.001$). There were also a significantly more nodules with a non-diagnostic result in the Group A (χ^2 test, $P < 0.001$) than in Group B (33% vs 25% respectively). The Benign lesions and follicular Neoplasm were significantly more frequent in Group B (59.1 and 1.5%) when compared to Group A (53.0 and 0.6%), (χ^2 test, $P < 0.001$ for benign lesions; $P < 0.05$ for follicular neoplasms). There was no significantly difference in the results of atypia of undetermined significance, suspicious for malignancy and malignant with or without CT.
Conclusions
The presence of a CT had an impact on results of FNAC, diminishing the number of non-diagnostic results and increasing the results of benign lesions and follicular neoplasms.

DOI: 10.1530/endoabs.37.EP911

EP912

Proprotein convertase subtilisin/kexin type 9 (PCSK9), soluble lectin-like oxidized ldl receptor 1 (SLOX-1) and ankle brachial index in short term overt hypothyroidism

Cigdem Ozkan[1], Mujde Akturk[1], Alev Eroglu Altinova[1], Ethem Turgay Cerit[1], Ozlem Gulbahar[2], Mehmet Muhittin Yalcin[1], Nuri Cakir[1] & Fusun Balos Toruner[1]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Gazi University, Ankara, Turkey; [2]Department of Biochemistry, Faculty of Medicine, Gazi University, Ankara, Turkey.

Cardiovascular deleterious effects of short term hypothyroidism are not well known. We aimed to investigate proprotein convertase subtilisin/kexin type 9 (PCSK9), soluble lectin-like oxidized LDL receptor 1 (sLOX-1) and ankle brachial index (ABI) in patients with thyroid cancer with short term overt hypothyroidism due to thyroid hormone withdrawal (THW). Twenty-one patients who require radioactive iodine (RAI) ablation or RAI scan and thirty-six age, sex, BMI similar euthyroid healthy control subjects were enrolled into this study. Patients were evaluated both in subclinical thyrotoxic period when they were on suppressive levothyroxine therapy and overt hypothyroidism period due to THW for four weeks. Serum PCSK9, sLOX-1, lipid levels and ABI were measured in patient and control groups.Total cholesterol, LDL cholesterol, triglycerides and Apo B levels were increased in short term overt hypothyroidism compared to control group ($P < 0.001$). Patients with short term overt hypothyroidism had significantly increased PCSK9 levels compared to control group ($P < 0.001$). PCSK9 levels were also found to be increased before THW when compared to control group ($P = 0.004$). sLOX-1 levels were not different between patients with short term overt hypothyroidism and control group ($P = 0.27$). ABI was found to be significantly decreased in patients with short term overt hypothyroidism compared to control group ($P = 0.02$). In conclusion, we found increased PCSK9 and decreased ABI which may contribute to the undesirable metabolic and vascular changes in thyroid cancer patients with short term overt hypothyroidism due to THW.

DOI: 10.1530/endoabs.37.EP912

EP913

Thyroid malignancy risk of incidental thyroid nodules in patients with non-thyroid cancer

Mehmet Yalcin[1], Alev Altinova[1], Cigdem Ozkan[1], Fusun Balos Toruner[1], Mujde Akturk[1], Ozgur Akdemir[2], Tugce Emiroglu[3], Derda Gokce[3], Aylar Poyraz[4], Ferit Taneri[5] & Ilhan Yetkin[1]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Gazi University, Ankara, Turkey; [2]Department of Nuclear Medicine, Faculty of Medicine, Gazi University, Ankara, Turkey; [3]Department of Internal Medicine, Faculty of Medicine, Gazi University, Ankara, Turkey; [4]Department of Pathology, Faculty of Medicine, Gazi University, Ankara, Turkey; [5]Department of General Surgery, Faculty of Medicine, Gazi University, Ankara, Turkey.

Objective
Thyroid incidentaloma is a common endocrinological disorder. Current literature regarding the risk of thyroid cancer in incidentalomas found in patients with non-thyroid cancer is limited. The aim of the present study was to investigate the frequency of thyroid malignancy in thyroid incidentalomas detected in patients with non-thyroid cancer.
Methods
The database of 287 thyroid nodules from 161 patients with a history of non-thyroid cancer followed between 2008 and 2014 were retrospectively evaluated.
Results
From 287 thyroid nodules, 69.7% had a benign final cytology. Thyroid cancer detected in one nodüle while follicular neoplasia detected in four nodules, atypia of unknown significance (AUS) detected in ten nodules, hurthle cell neoplasia detected in five nodules and suspicious for malignancy detected in six nodules according to fine needle aspiration biopsy results. Metastasis of the non-thyroid cancer to the thyroid gland were detected in four nodules. Twenty seven nodules from 15 patients were removed with surgery. There were three malignant nodules found after surgery (one papillary, one follicular and one medullary cancer). In addition to these three thyroid cancers, two patients with benign nodules had co-incidental thyroid cancer detected after surgery. Finally, 11.1% of thyroid nodules which underwent thyroid surgery had malignant histopathology except co-incidental and metastatic cancers.
Conclusion
The frequency of thyroid malignancy seems not to be substantially increased in incidental thyroid nodules detected in patients with non-thyroid cancer when these patients were evaluated in nodule-based approach.

DOI: 10.1530/endoabs.37.EP913

EP914

Differentiated thyroid cancer: assessment of clinical practice in a tertiary referral centre

Patrick Owens[1], Aoife Lowery[1], Denis Quill[1], Marcia Bell[2] & Michael Kerin[1]
[1]Department of Surgery, University Hospital Galway, Galway, Ireland; [2]Department of Endocrinology, University Hospital Galway, Galway, Ireland.

International best practice guidelines provide well-defined recommendations for the management of differentiated thyroid cancer (DTC) measuring ≤ 1 cm, > 4 cm and for those with defined risk factors. However, the extent of surgery and requirement for radioiodine remnant ablation (RRA) are less clearly defined for tumours 1–4 cm in size. Guidelines recommend a 'personalised decision making' approach for this cohort, with therapeutic decisions based on patient preference, recurrence risk and multi-disciplinary discussion. This study aims to assess adherence to guidelines and investigate treatment patterns in the 'personalised decision making' cohort for thyroid cancers in an Irish tertiary referral centre. A random subset of 97 patients treated for DTC between 2009 and 2014 were assessed. Data were obtained from a prospectively maintained thyroid cancer database. 92 out of 97 patients (95%) were managed in accordance with guidelines (Table 1). Out of those whose management did not adhere to guidelines, three were over treated with total thyroidectomy, while two were under treated with lobectomy only. 28 patients (29%) had tumour characteristics requiring 'personalised decision making', of which 26 underwent total thyroidectomy rather than lobectomy. Similarly for RRA, 39 out of 41 patients (95%) in the 'personalised decision making' group were treated with radioactive iodine.

Table 1.

	Patients (%)	Adherence to guidelines (%)
Total cohot:	97 (100)	92 (95)
≤ 1 cm	17 (18)	14 (82)
1–4 cm	61 (63)	61 (100)
> 4 cm	19 (20)	17 (89)
Multifocal	40 (41)	38 (95)
Lymphovascular invasion	21 (22)	20 (95)
Capsular invasion	21 (22)	21 (100)

These data suggest that management of thyroid cancer at our institution closely adheres to guidelines, with a trend towards more aggressive management in those where personalised decision making is required.

DOI: 10.1530/endoabs.37.EP914

EP915

Graves' disease and papillary/insular thyroid cancer in a large compressive goitre

Mara Carsote[1,2], Anda Dumitrascu[2], Dana Terzea[2,5], Andreea Geleriu[2], Dan Peretianu[3], Daniela Alexandrescu[2,4], Corina Chirita[6], Radu Iorgulescu[5], Andrei Goldstein[2] & Catalina Poiana[1,2]
[1]C. Davila University of Medicine and Pharmacy, Bucharest, Romania; [2]C.I. Parhon National Institute of Endocrinology, Bucharest, Romania; [3]SCM Povernei Medical Centre, Bucharest, Romania; [4]St John Hospital, Bucharest, Romania; [5]Monza Oncoteam Hospital, Bucharest, Romania; [6]Anima Medical Centre, Bucharest, Romania.

Introduction
The association between autoimmune thyroid disease and thyroid cancer is a dynamic field regarding the prevalence data and the common pathogenic background.
Aim
We report a sixth decade women case with a 1 year history of Graves' disease that was discovered with an aggressive differentiated thyroid carcinoma.
Case report
M.E. 56-year-old female has a 10 months history of daily medium dose of thyamazolum which was well tolerated (she presented with mild features of hyperthyroidism). The personal and family medical history is negative. On admission, she accused compressive symptoms for the last 2 months. The TSH was 1.59 μUI/ml. The eye examination showed values of 17 mm for proptosis. The cervical computed tomography pointed a large left thyroid nodule of 4.5 by 7.28 cm, with multiple microcalcifications associating a mass effect over the trachea (the minimum diameter of 1.71 by 1.7 cm at the level of clavicles). The eye exam showed values of 17 mm for exophthalmometria. The calcitonin was normal (of 0.857 pg/ml) , as well as antithyreoperoxidase antibodies (of 14 U/ml). The total thyroidectomy and lymph neck resection was performed. A papillary thyroid carcinoma (oxifile type) with insular and compact areas was found (of 6 cm), together with vessel invasion (T3N1Mo). The immunohistochemistry pointed a Ki67 of 15%. The 131 iodine therapy was added to the levothyroxine suppressive therapy.
Conclusion
The finding of a follicular cells cancer in a thyroid underling an autoimmune process is a rare event, yet new data reveals that the two diseases maybe more than incidental, possible by sharing common mechanisms.

DOI: 10.1530/endoabs.37.EP915

EP916

Differentiated thyroid carcinoma prevalence in the Graves' disease; Akdeniz University experience

Mustafa Kemal Balci, Birsen Unsal Koyuncu, Safiye Arık, Cumhur Arıcı, Ramazan Sarı & Hasan Ali Altunbaş
Akdeniz University Medical Faculty, Antalya, Turkey.

Objective
The frequency of differentiated thyroid cancer in the Graves' disease are controversial. The aim of this study was to evaluate the frequency of thyroid cancers in patients operated because of Graves' disease.

Subjects and methods
Sixty-six patients in whom thyroidectomy was performed because of Graves' disease between 2001 and 2012 were evaluated retrospectively. Patients who had received radioactive iodine treatment and external irradiation treatment in the neck region and who had had thyroid surgery previously were not included in the study.
Results
Thyroid nodule was absent in 17 (25.8%) of 66 Graves' patients. There was one thyroid nodule in 17 (25.8%) patients, two thyroid nodules in 13 (19.7%) patients, three thyroid nodules in 13 (19,7%) patients, four thyroid nodules in 4 (6.1%) patients, and five and over in 2 (3%) patients. Thirteen (19.7%) patients had thyroid cancer in the s patients. The rate of thyroid cancer was 17.6% ($n=17$) in the Graves' patients who had no nodule, whereas it was statistically not different from other graves patients with nodules. The risk of thyroid cancer didn't increased significantly in the presence of nodule.

DOI: 10.1530/endoabs.37.EP916

EP917

Association of papillary thyroid cancer with thyroid autoimmunity

Gesthimani Mintziori, Fotini Adamidou, Zoe Eustathiadou, Athanasios Panagiotou, Panagiotis Anagnostis & Marina Kita
Department of Endocrinology, Ippokratio General Hospital, Thessaloniki, Greece.

Introduction
Although the association between thyroid autoimmunity and papillary thyroid carcinoma (PTC) is supported by clinical studies, evidence to their pathophysiologic link and causal relationship is lacking. Moreover, there is a paucity of data regarding the association of thyroid autoimmunity with the less common types of differentiated thyroid cancer (DTC). The aim of the current paper was to investigate the association of autoimmunity and PTC vs follicular or medullary thyroid cancer.
Methods
We conducted a retrospective, registry-based study in the Department of Endocrinology, Ippokratio General Hospital, Thessaloniki, Greece. Patients with histologic evidence of DTC that were pre-operatively screened for thyroid autoimmunity during the last 5 years were included in the study. Patients with known cancer-related syndromes (patients with autoimmune polyglandular syndrome or multiple endocrine neoplasia) were excluded from the analysis. Thyroid autoimmunity was defined as presence of positive anti-TPO and/or anti-Tg antibodies. Statistical analysis was performed with the use of IBM SPSS 20.
Result
Sixty-five patients with thyroid cancer were assessed (12 men and 53 women). Their mean age was 51 ± 2 years. Out of 65 patients, 54 patients had PTC, six had follicular cancer and five patients had medullary cancer. When patients with PTC were compared with patients with follicular or medullary cancer, the prevalence of thyroid autoimmunity was higher in patients with PTC in comparison with patients with other types of thyroid cancer (43% vs 9% respectively, $P=0.035$), independently of TSH concentrations.
Conclusion
This small retrospective study demonstrates that patients with PTC demonstrate significantly higher prevalence of thyroid autoimmunity, in comparison with other types of DTC. Further study into this differential association may provide insights for better prevention and management of PTC.

DOI: 10.1530/endoabs.37.EP917

EP918

Evaluatıon of recurrence risk in differentiated thyroid cancer after treatment

Mustafa Koçak[1], Rahman Koseoglu[1], Bircan Sönmez[2], Serdar Türkyilmaz[3], Ismail Dogan[2], Halil Onder Ersoz[1] & Cihangir Erem[1]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey; [2]Department of Nuclear Medicine, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey; [3]Department of General Surgery, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey.

Introduction
The aim of this study was to validate the American Thyroid Association (ATA) risk of recurrence staging system (2009).
Methods
Retrospective analysed 300 adult (239 women, 61 men) differentiated thyroid cancer patients followed for a median of 57 months (range 38–97).
Results
ATA risk stratification of patients according to the system 54.7% low-risk, 39.7% moderate risk, and 5.7% were in the high risk group. The responses of patients to treatment; 79.7% very well to treatment, 11% acceptable, 9.3% of the showed that the response is missing. In 21% of patients follow-up of persistent or recurrent disease in the last case was detected. Initial treatment responses based on the persistent structural or recurrent disease adapted risk estimation in low risk group not treated very well responsive 7.3% from 2.9%, intermediate-risk group and the treatment very good responders and 14.3% from 5.3%, higher risk group and 70.5% in those who respond very well to therapy than was seen in 60%. In this study the first 2 years treatment criteria follow-up of disease status of being considering the low risk group treated very well not respond, intermediate-risk group, stimulated thyroglobulin <1 ng/ml or treatment very good response of the high-risk group is suppressed Tg$<$ 1 ng/ml of being, at the end of follow-up showed that disease estimated to be more powerful.
Conclusion
According to ATA risk classification, initially recurrent/persistent disease was found to be a useful system to predict. However, only adapted to the risk of follow-up the patient's entire life does not change during the initial risk estimates also showed that not be done. Tailored to each patient, to achieve dynamic and full of risk assessment, risk prediction system response to treatment is needed to conclude that the combination of the variables.

DOI: 10.1530/endoabs.37.EP918

EP919

Primary squamous cell carcinoma of the thyroid: a rare type of thyroid cancer

Pinar Sisman[1], Ahmet Bilgehan Sahin[2], Hande Peynirci[1], Ozen Oz Gul[1], Soner Cander[3], Erdinc Erturk[1] & Canan Ersoy[1]
[1]Uludag University Medical School Department of Endocrinology and Metabolism, Bursa, Turkey; [2]Uludag University Medical School Department of Internal Medicine, Bursa, Turkey; [3]Sevket Yilmaz Training anr Research Hospital Clinic of Endocrinology and Metabolism, Bursa, Turkey.

Introduction
Primary squamous cell carcinoma (PSCC) of thyroid is a rare type of thyroid malignancies because thyroid gland lacks squamous epithelium. It is seen in $<1\%$ of all thyroid malignancies. During last 30 years only about 90 cases were published. PSCC is an aggressive tumour as well as rare.
Case report
We present a 60-year-old female who had been followed up for multiple nodules in thyroid in our outpatient clinic for 2 years. Her serum free thyroxine (fT_4), free triiodothyronine (fT_3) and TSH levels were 0.9 ng/dl, 1.8 pg/ml, and 3.8 μIU/ml, respectively Her first fine needle aspiration cytology (FNAC) was benign. During follow-up because of sonographic features of nodul in left lobe, we performed the second FNAC which was suspicious for malignancy. Then total thyroidectomy was performed. In histopathological examination, well differentiated squamous cell carcinoma was revealed. Lymphovascular invasion was not seen. After surgery there was no increased glucose metabolism on F-18-fluorodeoxyglucose positron emission tomography. 21 months have passed after surgery and she had no complaint. She is going on the follow-ups.
Conclusion
PSCC of thyroid is rare but aggressive malignancy comparing with other thyroid cancers. FNAC is important for diagnosis like other types. It seems complete surgical eradication of tumour is the main treatment in PSCC of thyroid. But to achieve this, early and accurate diagnosis is important.

DOI: 10.1530/endoabs.37.EP919

EP920

Series of cases a descriptive study of management of metastatic medullary thyroid cancer

Eyvee Arturo Cuellar Lloclla, Mariana Tome Fernandez Ladreda, Guillermo Martinez de Pinillos Gordillo, Mariola Mendez Muros, Juan Manuel Garcia de Quiroz, Ignacio Fernandez Peña, Fernando Garcia Perez, Ignacio Fernandez Lopez, Margarita Rivas Fernandez, Juana Hidalgo Amat & Maria Victoria Cozar León
Hospital Virgen del Valme, Seville, Spain.

Introduction
There are new therapies indicated in medullary thyroid cancer (MTC) based on different molecular targets, that appear to be effective in some cases with advanced disease, although many are still under investigation.
Material and methods
We retrospectively evaluated five cases of medullar thyroid advanced carcinoma that later were referred to Oncology Department for Chemotherapy treatment.
Results
Five patients (mean age 52 ± 18.8 years) were evaluated. All cases were sporadic and stage IV at diagnosis. Four cases had undergone total thyroidectomy and cervical lymphadenectomy. three patients had metastases at diagnosis, the other two patients persistent with local disease after surgery. The average value of calcitonin prior to the oncology evaluation was 3072.6 ± 3789.6 pg/ml (382–8600 pg/ml) and CEA 576.5 ± 856.9 ng/ml (13.23–2075 ng/ml). Threeout of five patient received chemotherapy (Vandetanib). The average decrease in calcitonin and CEA in treated patients was 1350 ± 2448.8 pg/ml (−240 to 4170 pg/ml) and 1862.3 ± 1009.1 (−275 to 1714 ng/ml). None of them showed advanced disease on different imaging studies, and two of them had mild radiological improvement. Two untreated patients had showed a mean increase of calcitonin and CEA of 377 pg/ml and 10.3 ng/ml; in both cases the radiologic stability of the disease remained in time. Only one patient had cutaneous toxicity with Vandetanib.
Conclusions
Patients with Vandetanib had certain laboratory and radiologic improvement, although more investigation of the long-term efficacy would be necessary. In our study, patients with asymptomatic metastatic MTC disease had persisted with radiologic and analytical stability despite not chemotherapy applied. These data are consistent with current recommendations about not to treat patients with these characteristics.

DOI: 10.1530/endoabs.37.EP920

EP921

Identification of high-risk patients with incidental papillary microcarcinomas of thyroid helps in deciding appropriate management

Naveen Siddaramaiah, Mamatha Devaraj, Satish Artham & Sathyajith Nag
South Tees Hospitals NHS Foundation Trust, Middlesbrough, UK.

Papillary microcarcinoma (PMC) of thyroid is being increasingly detected following thyroid surgery for various reasons. The management of incidental PMC, not clinically or radiologically evident, is not well defined often leading to over treatment. Identifying risk factors for recurrence could help in administering appropriate management.
Aims and methods
To review the incidence of PMC and management locally. Retrospective review of case notes of patients diagnosed with papillary carcinoma over 9 years (2006–2014).
Results
$n = 113$, of which 30 were PMC (26.5%). Female = 23. Mean age: 49 years. Lump in the neck was the commonest initial presentation. Patients had one FNAC on an average (Thy3 to Thy5 $n = 11$). Nine patients with suspicious or diagnostic cytology or non-thyroidal surgeries were excluded. 21 patients had incidental PMC (total thyroidectomy $n = 7$, lobectomy $n = 14$). Five patients underwent completion thyroidectomy and further foci of PMC were found in three of them. Eight out of 21 patients were found to have risk factors such as size (6–10 mm), multifocality, and extrathyroidal spread. Five of eight patients had initial total thyroidectomy. Three underwent hemithyroidectomy followed by completion thyroidectomy. Completion thyroidectomy was done in one patient (MEN1) without risk factors for incidental PMC in thyroid tissue attached to parathyroid specimen. Five of 21 patients received radioiodine ablation following surgery ($n = 4$ with risk factors, $n = 1$ oncocytic neoplasm). 19 patients received post-operative hormonal therapy including eight with risk factors. TSH level was aimed at 0.1–0.4 mU/l. Complete suppression of TSH was noted at various stages during follow up in four of these 19 patients (21%).
Conclusion
Incidence of PMC in this cohort is in keeping with published literature. Identifying risk factors for local or regional recurrence is helpful in optimising management of incidental PMC. This could avoid unnecessary overtreatment with extensive surgery or RAI ablation or TSH suppression.

DOI: 10.1530/endoabs.37.EP921

EP922

Incidence of intrathyroid location of parathyroid glands and description of their characteristics compared to extrathyroid ones

Nick Michalopoulos[1], Efterpi Margaritidou[2], Efstathios Kotidis[1], Konstantinos Sapalidis[1], Ioannis Kanellos[1] & Kalliopi Pazaitou Panayiotou[2]
[1]3rd Department of Surgery, Aristotle University of Thessaloniki, AHEPA University Hospital, Thessaloniki, Greece; [2]Department of Endocrinology, Endocrine Oncology, Theagenio Cancer Hospital, Thessaloniki, Greece.

Introduction
Total thyroidectomy (TT) is a safe and effective operation. The most frequent complication after TT is hypoparathyroidism. Surgical trauma, devasculisation of parathyroid glands and inadvertent parathyroidectomy have been identified as the main causes resulting in postoperative hypocalcaemia. The objectives of this study are to investigate the incidence of intrathyroid parathyroid glands (ITPGs) in a large cohort and to clarify their histological characteristics.
Patients and methods
This is a retrospective study of two specialized centers in thyroid diseases. The medical records of patients with thyroidectomy were reviewed. Patients who underwent lobectomy or near total thyroidectomy, intentional parathyroidectomy during TT for concurrent parathyroid diseases, lymph node dissection and patients with inadequate data were excluded from the study. Patients were divided into two groups: those with (P group) and those without parathyroidectomy (non-P group). According to the location of the dissected parathyroid gland the P-group was sub-divided in ITPGs or extrathyroid parathyroid glands (ETPGs). Morphological characteristics of ITPGs were compared with the corresponding characteristics of the ETPGs in a case control way.
Results
4500 patients with TT were included. 605 of them were excluded from the study. Inadvertent parathyroidectomy (IP) was presented in 424 cases (10.89%). Intrathyroid parathyroid glands were presented in 68 cases (1.75%). There was a trend of ITPGs being smaller in size compared to ETPGs ($P = 0.067$). Cystic degeneration was presented in ITPGs ($P = 0.01$). Other histological characteristics, including weight were similar in intra and extra parathyroid glands. Presence of clinical hypocalcaemia was similar in all groups.
Conclusions
The incidence of ITPGs in our cohort is 1.75%. Surgical removal of ITPGs does not increase the presence of clinical hypocalcaemia and should be consider a minor complication of TT. Patients should be informed prior to TT about the possible presence of ITPGs and, therefore, their probable accidental removal.

DOI: 10.1530/endoabs.37.EP922

Thyroid (non-cancer)

EP923

Histopathological results of suspicious nodules in the patients with Hashimoto thyroiditis

Sevilay Ozmen[1], Ilknur Calik[1], Yusuf Can[1], Ozge Timur[2], Ayse Carlioglu[3], Hakan Sevimli[2], Senay Arikan Durmaz[3], Esref Kabalar[1] & Kenan Cadirci[2]
[1]Department of Pathology, Erzurum, Training and Reserch Hospital, Turkey; [2]Department of Internal Medicine, Training and Reserch Hospital, Erzurum, Turkey; [3]Department of Endocrinology, Training and Reserch Hospital, Erzurum, Turkey.

Introduction and aim
The most endocrinologists in routine practice are used to Bethesda classification for evaluation of thyroid nodule in fine needle aspiration biopsy (FNA). It is accepted that FNA biopsy is an accurate diagnostic and gold standard test. However, false-positive diagnosis may sometimes occur as a patient with a 'malign' lesion is found incorrectly rather than an actually benign lesion on histological examination. Hashimoto's thyroiditis probably is the most common cause of false-positive cytology. The aims of present study evaluate retrospectively postoperatively biopsy results in patients with Hashimoto disease have a thyroidectomy.
Materials and methods
Results of totally 29 patients with Hashimoto thyroiditis achieved from our hospital records. All of the patients had undergone totally or subtotals thyroidectomy. We re-evaluated retrospectively biopsy results postoperatively. We compared their preoperative FNA results.
Results
We detected 24.1% papillary thyroid cancer in seven patients (mean age 45.5 ± 11.9 year), 44.8% nodular goitre in 13 patients (mean age 45.8 ± 4.9 year), 13.7% adenomatous nodule in four patients (mean age 43.5 ± 14.4 year), 3.4% hurtle cell adenoma in one patient with 56 years old. But, 14% in four patients with Hashimoto thyroiditis (mean age 41.5 ± 13.1 year) were redundantly operated due to atypia of undetermined significance in FNA.
Conclusions
Although Hashimoto disease is a benign diagnosis, its misclassification as atypia of undetermined significance in FNA accounts for some false-positive errors. The cytopathologists can frequently be interpreted as atypia of undetermined significance instead of Hashimoto's thyroiditis. Therefore, result of atypia of undetermined significance in FNA may lead unnecessarily concern among with the endocrinologists. More importantly, our results demonstrated that high papillary thyroid cancer rate was found postoperatively in suspicious nodules evolved background Hashimoto thyroiditis.

DOI: 10.1530/endoabs.37.EP923

EP924

The evaluation of demographic features and histopathological results in patients with reoperative thyroid surgery

Fatma Neslihan Cuhaci[1], Husniye Baser[2], Cevdet Aydin[1], Aylin Kilic Yazgan[3], Seyda Turkolmez[4], Mehmet Kilic[5], Reyhan Ersoy[1] & Bekir Cakir[1]
[1]Department of Endocrinology and Metabolism, Yildirim Beyazit University Faculty of Medicine, Ankara, Turkey; [2]Department of Endocrinology and Metabolism, Ataturk Education and Research Hospital, Ankara, Turkey; [3]Ataturk Education and Research Hospital, Department of Pathology, Ankara, Turkey; [4]Department of Nuclear Medicine, Ataturk Education and Research Hospital, Ankara, Turkey; [5]Department of General Surgery, Ataturk Education and Research Hospital, Ankara, Turkey.

Introduction
Reoperative surgery for thyroid disease is rare. It is sometimes indicated for nodular recurrence after partial surgery for initially benign thyroid disease or for a completion total thyroidectomy when a final diagnosis of thyroid cancer is confirmed on a permanent section of a partially removed thyroid gland. We aimed to investigate the demographic features and reoperation indications in patients with reoperative thyroidectomy.
Methods
Thirty-six patients reoperated between 2008 and 2011 were included into the study. Demographic features, indications of reoperation and histopathological results of patients were evaluated retrospectively.
Results
After reoperative thyroidectomy, the results of histopathological evaluation of 24 patients were malignant (19 papillary thyroid carcinomas, three follicular thyroid carcinomas, one Hurthle cell neoplasm and one neoplasm with undetermined malignant potential) while 12 patients were benign. Of 36 patients, 11 (30.5%) went to reoperation due to giant thyroid nodule (>4 cm), 5 (13.9%) due to ≥2 nondiagnostic fine needle aspiration biopsy (FNAB), 3 (8.3%) due to toxic multinodular goitre, 5 (13.9%) due to malignant cytology, 2 (5.6%) due to suspected malignancy, 2 (5.6%) due to suspicion for a follicular neoplasm, 3 (8.3%) due to follicular lesion of undetermined significance, 1 (2.8%) due to atypia of undetermined significance, 1 (2.8%) due to suspected Hurthle cell neoplasm and 3 (8.3%) due to cytology of cellular adenomatoid nodule and ultrasonography suggesting malignancy.
Conclusion
Thyroid surgery may lead to regional scars and some degree of fibrotic process. This may result in problems in collecting thyroid FNAB samples and assessing cellular abnormalities. Our study findings demonstrated that histopathological evaluation of 14 patients whose cytological results showed no malignancy, was consistent with malignancy. We consider that decision for reoperative thyroidectomy should not be made with cytological findings, but patients' symptoms and ultrasound findings should also be taken into account.

DOI: 10.1530/endoabs.37.EP924

EP925

A case of primary hypothyroidism initially presenting with massive pericardial effusion

Mahmut Apaydin[1], Selvihan Beysel[1], Taner Demirci[1], Erman Çakal[1] & Tuncay Delibasi[1,2]
[1]Department of Endocrinology and Metabolism, Diskapi Yildirim Beyazit Teaching and Research Hospital, Ankara, Turkey; [2]Department of Internal Medicine, School of Medicine (Kastamonu), Hacettepe University, Ankara, Turkey.

Introduction
Although pericardial effusion is a common finding in primary hypothyroidism, massive pericardial effusion or pericardial tamponade are rare. Herein, we describe a newly diagnosed case of primary hypothyroidism initially presenting with massive pericardial effusion.
Case report
A 64 years old male patient attended to the emergency unit with worsening dyspnea over the past 1 month. ECG showed a low voltage QRS wave. Chest X-ray showed increased cardio-thoracic index. No infiltration observed in the lung parenchyma. Massive pericardial effusion diagnosed by Echocardiography and ejection fraction was measured 60%. Pericardiocentesis was performed and a total of 2800 cc of fluid was evacuated. Complete blood count, rutine biochemical tests and erythrocyte sedimentation rate were normal. No bacterial growth was observed in pericardial fluid samples and cytological examination revealed no findings suggesting malignancy. Also, adenosine deaminase level was normal and no growth occurred in Lowenstein-Jensen medium. Rheumatoid factor, antinuclear antibody profile, and viral markers (HIV and HBsAg) were negative. Thyroid function tests were as follows: TSH >150 mIU/l (*n*: 0.5–4.7), fT_4 0.2 ng/dl (*n*: 0.8–1.7), fT_3 1.2 pg/ml (*n*: 1.8–4.6 pg/ml), antiTPO and antiTG negative. There were no findings in ultrasound examination of the thyroid gland. Consequently, a diagnosis of primary hypothyroidism was made and replacement treatment was initiated with 50 μg/day of levothyroxine with gradual dose titration. Follow-up examination after 6 months was normal and no pericardial effusion detected by echocardiography.
Conclusion
Massive pericardial effusion is a rare complication of hypothyroidism and patients frequently exhibit other signs and symptoms of hypothyroidism before the development of pericardial effusion. However, in the patient described herein, initial presentation involved massive pericardial effusion associated with dyspnea. Physicians should keep in their mind that massive pericardial effusion might precede overt symptoms of hypothyroidism.

DOI: 10.1530/endoabs.37.EP925

EP926

Usefulness of Body Adiposity Index % in comparison to body composition analyser parameters among patients with and without autoimmune thyroid diseases hospitalised on Endocrinology Department-preliminary report

Aneta Koszowska[1,2], Justyna Nowak[1,2], Anna Bronczyk Puzon[2,4], Karolina Kulik Kupka[5], Anna Dittfeld[3] & Barbara Zubelewicz Szkodzinska[2]
[1]Doctoral Study in the School of Pharmacy with the Division of Laboratory Medicine in Sosnowiec (Medical University of Silesia in Katowice), Katowice, Silesia, Poland; [2]Department of Nutrition-Associated Disease Prevention; Faculty of Public Health, Bytom, Silesia, Poland; [3]Doctoral study in the School of Medicine with the Division of Dentistry in Zabrze (Medical University of Silesia in Katowice), Bytom, Silesia, Poland; [4]Doctoral Study in the School of Health Care in Katowice (Medical University of Silesia in Katowice), Katowice, Silesia, Poland; [5]Doctoral study in the School of Public Health (Medical University of Silesia in Katowice), Katowice, Silesia, Poland.

Introduction
Anthropometric parameters such like BMI aren't suitable enough for each type of figure and leads to misinformation about body composition. Body Adiposity Index (BAI) is suggested as an alternative for BMI.
Aim
The aim of the study was to compare the usefulness of BAI in context to body composition parameters.
Materials and methods
The BAI index was calculated for 86 patients according to previously described formula. The patients were divided into three examined groups: autoimmune thyroid disorders (including Hashimoto disease, Graves Basedow disease) (AITD) ($n=40$), non autoimmunological diseases of thyroid gland like thyroid goiter (non AITD) ($n=16$), and controls without thyroid dysfunction ($n=30$). The body analysis was done in the morning in light clothes by specialist equipment with Medical Device Directive. Spearman's rank correlation was used. The collected data were statistically analysed, $\alpha=0.05$.
Results
The mean age in group with autoimmune thyroid diseases AITD was 46.5 ± 15.97, BAI $34.33\pm7.29\%$, the mean of age in group with non autoimmunological diseases was 43.75 ± 17, 81, BAI $34.03\pm6.25\%$ among patients without thyroid diseases the mean age was 28.17 ± 9.78, BAI $30.38\pm5.22\%$. In each group BAI correlates with parameters obtained from body analyzer. Strong positive correlation was observed between BAI and % amount of body fat in group of patients with AITD ($r=0.86$, $P=0.0000$), non AITD ($r=0.713$, $P=0.0001$), patients without thyroid diseases ($r=0.84$, $P=0.0000$). Positive correlations were also observed in each groups between BAI and free fatty mas, muscle mass ($P<0.05$). Strong negative correlation was observed between BAI and % of body fat in each group ($P<0.05$).
Conclusions
BAI could be useful tool for evaluation of patients percentage amount of fat. Moreover BAI could be used when patient weighing is difficult because the body mass is not used in formula. BAI as a new marker should be validated for proper use.

DOI: 10.1530/endoabs.37.EP926

EP927

Health-related quality of life is reduced in treated primary hypothyroidism and with lower fT_3/fT_4-ratio

Hannah C M van Loon, Hanneke J C M Wouters, Anneke Muller Kobold, Sandra N Slagter, Thera P Links, Melanie M van der Klauw & Bruce H R Wolffenbuttel
University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

Introduction
Despite adequate treatment with LT_4 monotherapy, many patients with primary hypothyroidism still report complaints, as this treatment can not exactly imitate the endogenous homeostasis. We examined whether the different domains of HR-QOL were affected by the existence of a thyroid disorder and use of LT_4 substitution, and whether a lower ratio of free triiodothyronine (fT_3)–free thyroxine (fT_4) could predict lower HR-QOL.
Methods
A total of 16 631 participants from the population-based LifeLines Cohort Study, of Western European descent and with normal TSH values (0.4–4.5 mU/l), were evaluated; 368 of them used LT_4 monotherapy. TSH, fT_4 and fT_3) were measured with electrochemiluminescent immunoassay on the Roche Modular E170 Analyzer. HR-QOL was assessed using the Short Form-36 questionnaire.
Results
Mean ($\pm$s.d.) age was 51 ± 13 years and BMI 26.9 ± 4.7 kg/m^2 in the LT_4 users, vs 43 ± 13 years and 25.5 ± 3.8 kg/m^2 in the non-users; 90% of LT_4 users were females. We observed considerably higher fT_4 and lower fT_3 levels in LT_4 users, with the fT_3/fT_4-ratio being 25% lower in LT_4 users, despite similar TSH levels in both groups. 50% of LT_4 users had a fT_3/fT_4-ratio which was below the 2.5th percentile of euthyroid individuals. LT_4 users reported poorer HR-QOL, the largest reduction was observed in physical functioning, bodily pain, general health and vitality. In the non-users, those in the lowest tertile of the fT_3/fT_4-ratio reported a significantly lower HR-QOL in the domains physical functioning, bodily pain, and general health compared to participants in the middle and highest tertile.
Conclusion
Patients treated with LT_4 monotherapy for primary hypothyroidism report low HR-QOL. In subjects not using LT_4, a lower fT_3/fT_4-ratio was associated with more impairments in HR-QOL.
Disclosure
This work was supported by NCHA, Netherlands Consortium for Healthy Ageing, Bio-SHaRE-EU, Biobank Standardisation and Harmonisation for research excellence in the European Union. Bioresource research impact factor BRIF4568.

DOI: 10.1530/endoabs.37.EP927

EP928

Assessment of vitamin D (25-OH vitamin D_3) concentration among patients with and without autoimmune thyroid diseases hospitalised on Endocrinology Department-preliminary report

Aneta Koszowska[1,2], Justyna Nowak[1,2], Anna Bronczyk Puzon[2,3], Anna Dittfeld[4], Karolina Kulik Kupka[5], Agata Kulpok[6] & Barbara Zubelewicz Szkodzinska[2]
[1]Doctoral Study in the School of Pharmacy with the Division of Laboratory Medicine in Sosnowiec (Medical University of Silesia in Katowice), Katowice, Silesia, Poland; [2]Department of Nutrition-Associated Disease Prevention; Faculty of Public Health, Bytom, SIlesia, Poland; [3]Doctoral Study in the School of Health Care in Katowice (Medical University of Silesia in Katowice), Katowice, Silesia, Poland; [4]Doctoral Study in the School of Medicine with the Division of Dentistry in Zabrze (Medical University of Silesia in Katowice), Katowice, Silesia, Poland; [5]Doctoral Study in the School of Public Health (Medical University of Silesia in Katowice), Katowice, Silesia, Poland; [6]Department of Endocrinology, Country Hospital, Piekary Slaskie,Silesia, Poland.

Introduction
Vitamin D is important for proper functioning of all body tissues. Receptors for vitamin D are also presence in thyroid gland. It's open questions how this vitamin could modulate the thyroid function.
Aim
The aim of the study was assess the concentrations of vitamin D as well as antiTPO level among patients with thyroid dysfunction hospitalised on Endocrinology Department.
Materials and methods
The study was conducted among 86 patients, which were divided into three groups: Autoimmune Thyroid Disorders AITD (including Hashimoto disease, Graves Basedow disease) ($n=40$), non autoimmunological diseases of thyroid gland (e.g. thyroid goitre) ($n=16$), and persons without thyroid dysfunction ($n=30$) as control group. The Kruscal Wallis test and Spearman rank correlation were used. The collected data were statistically analysed, $\alpha=0.05$.
Results
The mean age in group with autoimmune thyroid diseases AITD was 46.5 ± 15.9, mean of antiTPO was 316.79 ± 303.94 IU/ml, vitamin D $18{,}53\pm9{,}17$ ng/ml. The mean of age in group with non autoimmunological diseases was 43.75 ± 17.81, antiTPO 0.63 ± 1 IU/ml, vitamin D 18.3 ± 7.42 ng/ml and among patients without thyroid diseases the mean age was 28.17 ± 9.78 and antiTPO 0.57 ± 0.98 IU/ml, vitamin D 16.54 ± 5.51 ng/ml. The statistical significance difference was observed between groups according to age ($P=0.0000$) and antiTPO level ($P=0.0000$), the statistical difference wasn't observed between vitamin D concentration in analysed groups. In all group of 86 patients positive correlation between age and antiTPO level was observed ($P=0.00003$). Obesity was most frequently observed among patients with AITD. The vitamin D deficiency defined as level below 20 ng/ml was observed among 71% all of hospitalized patients.
Conclusions
Screening of thyroid function should be done among patients with overweight, obesity and also among patients over 40. Vitamin D deficiencies should be diagnosed and corrected according to guidelines recommended in Central Europe.

DOI: 10.1530/endoabs.37.EP928

EP929

Renal involvement in Graves' disease patients treated with Benzylthiouracyl

Ibtissem Oueslati[1], Amel Melki[1], Hayet Kaaroud[2], Ibtissem Ben Nacef[1], Nadia Mchirgui[1], Karima Khiari[1] & Néjib Ben Abdallah[1]
[1]Department of Endocrinology, Charles Nicolle University Hospital, Tunis, Tunisia; [2]Department of Nephrology, Charles Nicolle University Hospital, Tunis, Tunisia.

Introduction
Renal complications in Graves' disease are rare and may be related either to the disease itself or secondary to antithyroid drugs.
Methods
We report seven cases of renal damage in patients with Graves' disease treated with Benzylthiouracyl collected over a period of 14 years.
Results
There were seven women with a mean age of 37.86 ± 14.25 years (19–61 years). Six patients developed renal vasculitis associated with ANCA. The signs were dominated by renal proteinuria and renal failure noted in all cases and associated with hematuria in five cases. The lung involvement was the most common extrarenal manifestation occurred in four patients (alveolar hemorrhage in two cases, lymphocytic alveolitis in one case and pleurisy in 1 case). The benzylthiouracyl was discontinued in four patients still under treatment. Corticosteroid therapy was used alone or in combination with cyclophosphamide in all cases. Plasmapheresis sessions were made during the alveolar hemorrhage. A complete remission was obtained in one case and incomplete remission in two cases. The other three patients required chronic hemodialysis. One patient died of sepsis. The seventh patient developed a nephrotic syndrome with hypertension and hematuria related to membranous glomerulonephritis. In this patient, the etiology was not found. Complete remission of nephrotic syndrome was achieved with corticosteroids.
Conclusion
The possibility of renal impairment in Graves' disease requires monitoring to detect urinary abnormalities in order to early initiate therapy and improve patient's outcome.

DOI: 10.1530/endoabs.37.EP929

EP930

Indications and outcomes of repeated thyroid fine-needle aspirations: a retrospective evaluation from a tertiary centre

Sevde Nur Firat, Ozlem Turhan Iyidir, Mehlika Isildak, Cüneyd Anil, Nazli Kirnap Gursoy, Asli Nar & Neslihan Bascil Tutuncu
Department of Endocrinology and Metabolism, Baskent University Hospital, Ankara, Turkey.

Introduction
Fine needle aspiration (FNA) is the first-line diagnostic test for evaluating thyroid nodules. This test can effectively distinguish between neoplastic and non neoplastic nodules. The Bethesda System suggest that thyroid nodules with non diagnostic (ND), atypia/follicular lesions of undetermined significance (A/FLUS) aspiration should undergo repeat sampling. We aimed to investigate the clinical validity of repeated FNA in the management of patients with thyroid nodules in our institution.
Methods/design
In this study we evaluated 668 nodules of 529 patients who undergone repeated sampling in Başkent University Hospital between 2000 and 2014.
Results
The majority of patients were female ($n=421$, %79.6). The mean age of patients was 60.1 ± 14.5 years. First evaluation revealed that 467 (89.9%) of nodules were benign, 180 (26.9%) were non diagnostic and 21 (3.1%) were A/FLUS). Enlargement of the nodule (%27.9) was the most common indication for a repeated sampling followed by non-diagnostic cytology (%26.9). Re-aspiration altered the initial diagnosis in 84.4% and 66.7% of the non-diagnostic and (A/FLUS) patients but only in 10.7% of patients with a benign cytology the initial diagnosis was changed. We evaluated the outcome of patients whose initial and repeated cytological diagnosis are non diagnostic and A/FLUS (Table 1). Outcome data was obtained 23 (65.7%) of these patients.

Table 1 Outcome data of patients with initial and repeated diagnosis of non diagnostic and A/FLUS.

FNA1–FNA2	Surgery	Repeated biopsy
ND-ND ($n=28$)	Nodular hyperplasia-6	Benign-7
	Papillary thyroid ca-2	ND-1
A/FLUS ($n=7$)	Nodular hyperplasia-5	Benign-2

FNA, fine needle aspiration; ND, non-diagnostic; A/FLUS, atypia/follicular lesions of undetermined significance.

Conclusion
Repeat FNA is useful in cases whose initial diagnosis is non diagnostic or A/FLUS, but repeated aspiration for patients with an initial benign examination appears to not increase the expected likelihood of a malignant cytology.

DOI: 10.1530/endoabs.37.EP930

EP931

The efficacy of radioiodine therapy in patients with non-toxic nodular goitre with large cold nodule

Saeid Abdelrazek[1], Piotr Szumowski[1], Katrzyna Siewko[2], Janusz Mysliwiec[1], Malgorzata Szelachowska[2] & Marcin Garkowski[1]
[1]Department of Nuclear Medicine, Medical University of Bialystok, Bialystok, Poland; [2]Department of Endocrinology, Diabetology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland.

Most of the patients with the benign cold nodule refuse surgical operation. Radioiodine therapy (RIT) is the choice for these patients. The aim of our study was to evaluate the efficacy of radioiodine therapy to reduce thyroid volume in patients with cold nodule by the use of two doses of radioiodine.
Methods
We treated 40 patients with non-toxic nodular goitre with large cold nodule, aged 18 and 48 years; initial 24 h radioiodine uptake (RAIU) was ranged between 18–45%, and thyroid volume ranged between 48 and 120 ml, effective half-life was more than 3 days at the time of treatment. Malignant changes were excluded in all nodules by fine needle aspiration biopsy. The activity dose was calculated by the use of Marinelli's formula and ranged between 280 and 800 MBq. Thyroid ultrasonography, and thyroid scan with RAIU at 24 was done before and after 6 and 12 months of RIT. Follow up control was done every 6 weeks.
Results
After 6 months RIT in all the patients the large cold nodule changes to hot nodule. In 13 patients the size of the thyroid gland decrease to 48%, and no need for the second dose of radioiodine therapy. 27 patients received second dose of RIT to decrease the nodule which was cold and turned to hot after the first dose. After 12 months of the second dose of radioiodine a mean thyroid volume reduction of 56% was achieved. After 12 months of RIT euthyroidism persist in 52% of patients, and hypothyroidism develop in 48% of patients.
Conclusions
Radioiodine is non-invasive, safe and cost effective method of therapy for reduction of large non-toxic goitre even with cold nodule. The reduction of the cold nodule and the thyroid volume, were due to well accurate measurement of administered activity, relatively high effective half-life and well-organised follow up.

DOI: 10.1530/endoabs.37.EP931

EP932

Fibromyalgia in patients with euthyroid Hashimoto's thyroiditis

Muge Bilge[1], Mine Adas[2], Muyesser Nergiz Yanmaz[3] & Aysen Helvaci[1]
[1]Okmeydani Education and Research Hospital, Internal Medicine, Istanbul, Turkey; [2]Okmeydani Education and Research Hospital, Endocrinology, Istanbul, Turkey; [3]Kemerburgaz University, Rheumatology, Istanbul, Turkey.

Introduction
The aims of this study are to evaluate fibromyalgia (FM) in patients with euthyroid Hashimoto's throiditis (HT) and whether antithyroperoxidase antibody (TPOAb) positivity is associated with the FM.
Methods
We have studied 167 patients with HT and 83 healthy controls followed in our hospital. Single researcher took the history and did physical examination including manual tender point examination according to Manuel Tender Point Survey instructions. For the diagnosis FM, 2010 American College of Rheumatology Classification Criteria for the FM was used. Thyroid assessment was done by free T_4, free T_3, TSH, antithyroglobulin antibody (TgAb) and TPOAb. Patients were excluded from the study if they had any other serious disease, and if there was any history of drug use that interferes with the symptoms of FM.

Results
FM was found in 40% (67 out of 167 patients) of in HT patients, in 7% (six out of 83 healthy controls, $P<0.001$) of controls. The average age was significant higher in patients with FM than controls (43.78±10.48 years vs 40.43±10.52 years, $P=0.02$). TSH (2.97±2.03 vs 2.20±1.33, $P=0.001$), TPOAb (240.92±268.6 vs 197.05±288.14, $P=0.006$) and TgAb levels (300.68±528.79 vs 153.76±411.51, $P=0.003$) where notable higher in patients with FM, according to patients without FM. Widespread pain index, symptom severity scale and tender point examination showed no significant difference between the patient and control group. On the other hand widespread pain index, symptom severity scale and tender point examination showed a positive correlation with TSH (r: 0.184, $P=0.004$; r: 0.204, $P=0.001$; r: 0.167, $P=0.009$, respectively). Also TgAb showed positive correlation with symptom severity scale (r: 0.168, $P=0.02$). İncreasing age in patients with HT showed positive relationship with widespread pain index and tender point examination($r=0.193$, $P=0.012$ and $r=0.170$, $P=0.02$ respectively).
Conclusion
In our study, euthyroid HT patients showed significantly higher prevalence of FM, as compared to healthy control. This finding support thyroid autoimmunity may influence the development of FM, but the evidence which support that FM is related to autoimmune aetiology is not clear, and FM severity may not be affected by the presence of thyroid autoantibody.

DOI: 10.1530/endoabs.37.EP932

EP933

False positive post RAI scan in a subject with papillary thyroid cancer secondary to urine contamination

Sebnem Aydin[2], Nafiye Direktor Ozmen[3], Umut Mousa[1], Osman Koseoglulari[1] & Hasan Sav[1]
[1]B Nalbantoglu Hospital Department of Endocrinology and Metabolism, Nicosia, Cyprus; [2]B Nalbantoglu Hospital Department of Nuclear Medicine, Nicosia, Cyprus; [3]B Nalbantoglu Hospital Department of Internal Medicine, Nicosia, Cyprus.

Introduction
Radioactive iodine (RAI) for remnant ablation and post RAI scanning are very frequently employed modalities in differentiated thyroid cancers (DTC). Radioactive iodine is secreted into physiological secretions such as tears and urine. In this case report we present a case who received RAI for DTC with a surprising post RAI scan compatible with multiple metastases.
Case report
A 53-year-old male subject underwent total thyroidectomy and ipsilateral lymph node dissection after being diagnosed as papillary thyroid cancer (PTC) via fine needle aspiration cytology (FNAC). He received 150 mCI of RAI due to lymph node metastases. His stimulated thyroglobulin level (Tg) was 33.3 ng/ml and was positive for anti thyroglobulin antibodies. In the post RAI scan we visualized suspicious metastases in the thyroidal area together with the mid abdominal, proximal right femoral, mid left femoral and distal left tibia areas. The metastatic findings were untypical and were localized anteriorly. Also the patients' general situation was fine so we planned a bone scan and PET CT to confirm these findings. Both bone scans and FDG PET was negative for metastases. The subjects' socioeconomic status and personal hygiene was very low thus we suspected these findings were secondary to urine contamination. Six months later he underwent a whole body scan which was negative for metastases. His stimulated Tg was 1.16 ng/ml and anti Tg was positive during the scan.
Discussion
Post RAI scanning is a very important technique for determining metastases in subjects with DTC. Contamination with body fluids can cause false metastatic findings in which other radiological methods and personal history can aid the physicians in making a decision.

DOI: 10.1530/endoabs.37.EP933

EP934

Smoking associated with TSH receptor antibody and serum IL17A elevation in hyperthyroid Graves' disease

Ildikó Molnár[1], Ilona Bohaty[2] & Éva Somogyiné-Vári[1]
[1]EndoMed, Immunoendocrinology and Osteoporosis Centre, Debrecen, Hungary; [2]Regional Centre of Hungarian National Blood Transfusion Service, Debrecen, Hungary.

Th17 cells represent newly discovered CD4+T cells producing predominantly IL17A cytokines, which are involved in inflammations and autoimmune diseases. Elevated IL17 levels were demonstrated in thyroid autoimmunity and the activity of Graves' ophthalmopathy. The relationship among IL17A, anti-thyroid antibodies, smoking, and clinical activity score of ophthalmopathy was investigated in hyperthyroid Graves' disease. One hundred and thirty-eight patients, 62 with Graves' disease (25 with ophthalmopathy, 33 with hyperthyroidism, and 17 have daily smoking), 38 with Hashimoto's thyroiditis and 38 healthy controls were investigated. Serum IL17A levels were measured with ELISA; thyroid hormones, anti-thyroid antibodies in a fully automated way, but TSH receptor antibodies with RIA. IL17A serum levels were higher in Graves' patients than those in Hashimoto's thyroiditis and controls (5.28±3.8 with or 5.43±3.62 ng/ml without ophthalmopathy vs 3.65±2.22 ng/ml, $P<0.04$ or $P<0.01$, respectively, for Hashimoto's thyroiditis and vs 2.83±0.73 ng/ml, $P<0.0001$ and 0.004 respectively for controls). Smoking increased IL17A levels in comparison with nonsmoking patients in hyperthyroid Graves' patients after thyrostatic therapy (2.92±1.44 ng/ml vs 10.46±7.18 ng/ml, $P<0.04$). TSH receptor antibody positive and hyperthyroid smoking patients showed significantly higher IL17A and TSH receptor antibody levels than those who were nonsmoking (3.59±2.28 ng/ml vs 7.24±5.42 ng/ml, $P<0.02$ for IL17A and 9.07±9.39 U/l vs 22.52±11.48 U/l, $P<0.01$ for TSH receptor antibodies). No relevant elevation in IL17A levels was connected to clinical activity score of ophthalmopathy. The results highlight the role of IL17A levels in hyperthyroid Graves' disease. Smoking can play as an aggravating factor in IL17A and TSH receptor antibody elevation.

DOI: 10.1530/endoabs.37.EP934

EP935

Evaluation of acoustic voice analysis in patients with subclinical thyrotoxicosis

Taner Demirci[1], Mehmet Uyar[2], Emel Tatar Çatallı[3], Mustafa Çalışkan[1], Bekir Uçan[1], Dilek Demiral[2], Müyesser Sayki Arslan[1], Mustafa Özbek[1], Mehmet Hakan Korkmaz[3] & Tuncay Delibaşı[1,4]
[1]Department of Endocrinology and Metabolism, Dişkapi Yildirim Beyazit Teaching and Research Hospital, Ankara, Turkey; [2]The Audiology–Speech Impediment Unit, Dişkapi Yildirim Beyazit Teaching and Research Hospital, Ankara, Turkey; [3]Department of Otolaryngology, Ministry of Health, Dişkapi Yildirim Beyazit Teaching and Research Hospital, Ankara, Turkey; [4]Department of Internal Medicine, School of Medicine (Kastamonu), Hacettepe University, Ankara, Turkey.

Introduction
The relationship between hyperthyroidism and voice disorders has not been identified before. The aim of this study was to investigate the changes in the acoustic values in patients with subclinical thyrotoxicosis.
Methods
In this study, acoustic voice analysis was evaluated in a total of 115 cases. Sixty of 115 individuals (18 men and 42 women) had subclinical thyrotoxicosis, aged between 18 and 65 years, and all had no history of laryngeal surgery, no vocal complaints. These patients were compared with the control group consisting of 55 cases (18 men and 37 women) with similar characteristics. Acoustic and perceptual analyses are the most commonly used method in the assessment of voice quality. Kay CSL 4300 unit was used for acoustic voice analysis and as the operating parameters, F0 (fundamental frequency), Jitter, Rap (relative average perturbation), Shimmer, noise-to-harmonic ratio (NHR), and voice turbulence index (VTI) values were evaluated. The results were evaluated using the Mann–Whitney U statistical method.
Results
The performed acoustic analysis showed that mean values of the investigated parameters in patients were Jitter (%) 1.18, Shimmer (%) 4.00, Rap (%) 0.70, F0 (Hz) 209.85, VTI 0.05, and NHR (dB) 0.14. In the control group, the analyzed parameters were the following: Jitter (%) 0.96, Shimmer (%) 3.16, Rap (%) 0.57, F0 (Hz) 207.86, VTI 0.05, and NHR (dB) 0.12. There was no statistically significant difference between the control group and patients ($P>0.05$).
Conclusions
In our study, it was concluded that the moderate increase in thyroid hormones doesn't affect the voice quality. Effect on the voice quality of the excess of thyroid hormones, such as clinical thyrotoxicosis was not evaluated. Therefore, further studies are needed to interpret the relationship between thyroid hormone and voice quality.

DOI: 10.1530/endoabs.37.EP935

EP936

Transient pulmonary hypertension in patients with Graves' disease

Hela Marmouch, Fadia Boubaker, Sondes Arfa, Tansim Slim, Hanene Sayadi, Manel Jmal & Ines Khochtali
Department of Internal Medicine and Endocrinology, Faculty of Medicine, Monastir, Tunisia.

Introduction
Hyperthyroidism produce changes in cardiac contractility, blood pressure, and systemic or pulmonary vascular resistance. In almost all cases these cardiovascular changes are reversible when the underlying thyroid disorder is recognised and treated. Pulmonary hypertension (PAH) has been associated with thyroid dysfunction, but primarily with hyperthyroidism. The vast majority of patients with this form of PAH are usually older with toxic multinodular goitre. The aim of this study was to determine the clinical correlates of PAH in patients with Graves' disease (GD).
Methods
Our study is retrospective one concerning patients with GD referred for echography before using any treatment. PAH has been diagnosis when pulmonary artery systolic pressure was elevated.
Results
Among 22 consecutive patients with GD referred for echocardiography, six patients (27.32%) had PAH measured by continuous-wave Doppler echocardiography (pulmonary artery systolic pressure >35 mmHg). The patients with PAH had significantly higher pulmonaryvascular resistance (PVR), cardiac output, and TSH receptor antibody (TRAb) compared to those without. Pulmonary artery systolic pressure may had a good correlation with TRAb, but was not related to free T_4. All this patients have a reversible pulmonary hypertension after treatment.
Discussion
In addition to the effect of thyroid hormone on the cardiovascular system, autoimmune-mediated pulmonaryvascular remodelling may play a role in Graves' disease-linked elevated pulmonary artery systolic pressure. An autoimmune process inducing endothelial damage with GD may play a key role. Future studies should focus on discovering the immunogenetic overlap between autoimmune thyroid diseases and PAH.
Conclusion
Study highlights the importance of considering hyperthyroidism as a cause of idiopathic PAH, and demonstrates the potential reversibility of its complications. At present, thyroid function tests should be considered in the investigation of all patients.

DOI: 10.1530/endoabs.37.EP936

EP937

Side effects of steroid therapy in Graves' orbitopathy: comparison of two different protocols: parenteral vs combined parenteral and oral

Biljana Beleslin, Jasmina Ciric, Mirjana Stojkovic, Slavica Savic, Slavica Ciric, Tijana Lalic, Tanja Nisic, Milos Stojanovic & Milos Zarkovic
Clinic for Endocrinology, Medical School, Clinical Center of Serbia, University of Belgrade, Belgrade, Serbia.

Introduction
Glucocorticoids (GCs) are the treatment of choice for moderate-to-severe and active Graves' orbitopathy (GO), but optimal treatment is still undefined as serious side effects are great concern of GC therapy. The aim of the present study was to evaluate tolerability and safety of two different treatment protocols.
Methods
Consecutive patients were divided according to the protocol of GC therapy into two groups: combined intravenous and oral GC therapy (combined GC group, 66 patients, 49 ± 10 years), and only intravenous GC therapy (IVGC group, 66 patients, 50 ± 11 years, $P=$NS). Combined GC therapy included 500 mg of methylprednisolone in 500 ml of saline solution for 2 alternative days, followed by oral prednisone tapering dose that was repeated each month for the next 5 months. Cumulative dose was 10.2 g. IVGC therapy included infusions of 500 mg of methylprednisolone for the first 6 weeks, and then infusions of 250 mg for the remaining 6 weeks. Cumulative dose was 4.5 g.
Results
Combined GC therapy induced significantly more side effects in comparison to IVGC (49/66, 74% vs 28/66, 42%, $P<0.001$), including weight gain of >3 kg (55% vs 22%, $P<0.001$), hirsutism in female patients (49% vs 4%, $P<0.001$), myalgias (33% vs 0%, $P<0.001$), sleeplessness (17% vs 2%, $P=0.004$), and urinary infections (15% vs 3%, $P=0.03$). Increase in total cholesterol (42% vs 35%) and development of diabetes (8% vs 3%) was also more prevalent without reaching statistical significance ($P=$NS). Considering serious side effects two patients in combined GC group developed herpes zoster infection and pulmonary tuberculosis, whereas one patient in IVGC group had myocardial infarction during IVGC therapy.
Conclusion
Side effects were more prevalent in the combined group, as a consequence of higher cumulative dose, longer duration of therapy (6 months vs 3 months), and treatment schedule. Careful monitoring during GC therapy in patients with GO is mandatory in both treatment protocols.

DOI: 10.1530/endoabs.37.EP937

EP938

Isolated cutaneous findings of systemic lupus erythematosus due to propylthiouracil

Gamze Erfan[1], Kaan Tasolar[1], Meltem Öznur[2] & Murat Yılmaz[3]
[1]Dermatology, Tekirdag, Turkey; [2]Pathology, Tekirdag, Turkey; [3]Endocrinology and Metabolism, Tekirdag, Turkey.

Propylthiouracil (PTU), used to treat thyroid dysfunctions such as Graves' disease, rarely induces lupus-like syndrome. A 52-year-old woman developed dermatological findings of systemic lupus erythematosus with malar rash, photosensitivity and discoid lupus erythematosus-like lesions, after 3 weeks of exposure to the drug. ANA and anti-dsDNA were positive. Skin biopsy of face revealed vacuolar changes in basal layer and lymphoid infiltration in perivascular region of dermis. No other organ involvement was diagnosed. PTU treatment was stopped and with oral prednisolone 40 mg daily, in 3 weeks she had resolution of lesions. The patient has no skin lesions in 2-month follow-up. This is a report of isolated skin findings of lupus-like syndrome with positive serologies and without any other organ involvement. The physicians should be aware of this rare but potentially serious, possible adverse effect of PTU.

DOI: 10.1530/endoabs.37.EP938

EP939

Seasonality in paediatric Graves' disease compared to the general population: impact of month of birth: a national study

Tiago Nunes da Silva, Bernardo Dias Pereira, Henrique Vara Luiz, Ana Catarina Matos, Maria Carlos Cordeiro, Luisa Raimundo & Jorge Portugal
Hospital Garcia de Orta – Endocrinologia e Diabetes, Almada, Portugal.

Paediatric Graves' disease (PGD) is an uncommon autoimmune disorder with a multifactorial origin. Although, in some autoimmune endocrinophaties the seasonality of month of birth (MOB) distribution differed from the general population, this association has not been study in PGD. The aim of this work was to analyse the impact of seasonality of MOB on PGD incidence in Portugal.
In 2013, the Portuguese Paediatric Society of Diabetes and Endocrinology undertook a national multicentric study of the PGD (153 cases). We compared the distribution of MOB within this study with the Portuguese population (data from the National Institute of Statistics). Since, the mean age at diagnosis was 11 years, we restricted the study period up to 2001 to correct for that variation (125 cases). Statistical analysis was performed with STATA Software, version 12.0. Walter and Elwood method was used because it takes into account the population at risk. A total of 125 cases of PGD born between 1983 and 2001 were recorded (75% females) compared to 2 271 523 births (49% females). Among PGD, the percentage of observed to expected births did not differ across the 12 months ($P=0.8$). Nevertheless, the smoothed birth-month estimates demonstrated a non-significant (NS) excess of births from September to April, and a deficit from May to July. The evaluation of the subgroup with higher TRABS titters at diagnosis (50 cases with TRABS ten times the upper limit of normal), did not show a higher incidence compared to the Portuguese population ($P=0.7$).
This was the first population-based study that analysed the impact of seasonality of MOB in the incidence of PGD. Despite a trend to a higher incidence of PGD in children born between September and April, no uniform seasonal pattern of MOB in PGD was observed in this sample of the Portuguese population. We thank the Portuguese Paediatric Society of Diabetes and Endocrinology for allowing the study data to be used in this work.

DOI: 10.1530/endoabs.37.EP939

EP940

Late onset of amiodarone-induced thyrotoxicosis causing pharmacoresistant atrial fibrillation with subsequent development of serious heart failure

Monika Nývltová, Karolína Drbalová, Patrik Jarkovský, Miroslav Vodák, Petr Krejcí & Miroslav Zavoral
Central Military Hospital, Prague, Czech Republic.

Amiodarone is a potent and among cardiologists still very popular anti-arrhythmic drug. This case report describes severe course of amiodarone-induced thyrotoxicosis (AIT) which is one of the most serious side effects of the treatment. The patient (J S born in 1950) was first hospitalised in June 2012 for atrial fibrillation with rapid ventricular response and tachycardia-induced cardiomyopathy with a decreased ejection fraction (EF). Thyroid hormones were normal at that time and electric cardioversion was successfully performed and following echocardiography showed improving EF. Attending cardiologist added to the medication amiodarone which was after <6 months discontinued for symptomatic corneal deposits. The second hospitalisation for the same reason was in September 2013. According to laboratory findings, ultrasonography and scintigraphy we diagnosed a destructive type of amiodarone-induced thyrotoxicosis more than half a year after the withdrawal of this drug! We started treatment with combined antithyroid medication at higher doses (including parenteral forms of administration) and corticosteroids. The atrial fibrillation was resistant to standard doses of β-blockers even in combination with digoxin. However, despite the normalisation of thyroid hormones the patient had to be after 33 days of treatment moved to ICU with a serious heart failure. After administration of levosimendan, diuretics and after an electric cardioverison was carried out, the clinical condition began to improve. We had decided for a total thyroidectomy and afterwards we started a substitution therapy with levothyroxine. Recurrence of atrial fibrillation in October 2014 was without any major concern quickly solved by pharmacological cardioversion with amiodarone. Nowadays, the amiodarone treatment was discontinued, the patient keeps sinus rhythm and a radiofrequency ablation is planned. This case report draws attention to the risk of developing a serious AIT even after a long time since discontinuation of administering amiodarone.

DOI: 10.1530/endoabs.37.EP940

EP941

Ultrasonography-guided fine-needle aspiration biopsies of thyroid nodules: single-centre experience

Salim Susuz[1], Nur Kebapci[2], Emine Dundar Kasapoglu[3], Mahmut Kebapci[4], Özge Cevikalp[5], Belgin Efe[2] & Aysen Akalin[1]
[1]Internal Medicine Clinic, Afyonkarahisar State Hospital, Afyonkarahisar, Turkey; [2]Endocrinology and Metabolism Division, Osmangazi University Medical School, Eskisehir, Turkey; [3]Pathology Division, Osmangazi University Medical School, Eskisehir, Turkey; [4]Radiology Division, Osmangazi University Medical School, Eskisehir, Turkey; [5]Statistic Division, Osmangazi University Medical School, Eskisehir, Turkey.

In the present study, we aimed to investigate the efficiency of ultrasound-guided fine-needle aspiration biopsy in our clinic. Totally, 701 patients followed at Department of Endocrinology, Faculty of Medicine, Eskisehir Osmangazi University with nodular thyroid disorder were included in this study during January 2000 and January 2011. Ultrasound-guided thyroid fine-needle aspiration biopsy was performed in these 701 cases at Interventional Radiology Department. Throid nodules were evaluated in terms of size, echo quality, peripheral halo, and calcification. The biggest diameter was determined measuring three dimensions of nodule. If multiple nodules were found in a patient, TFNAB was performed from the biggest dominant nodule. The result of US-TFNAB was insufficient in 11.7% of patients. US-TFNAB was reported as benign in 79.3% of patients, suspected malignant in 4%, malignant in 3.9% and suspected follicular neoplasm in 1.1%. When suspected follicular neoplasm and suspected malignancy cases were included into malignant group, the malignancy ratio based on US-TFNAB was 9%. 146 of 701 cases were operated (20.8%), 19 cases (2.7%) didn't accept the surgery. According to histopathology results of operated patients, 66 patients were malignant and 80 were benign (Table 1). No significant gender difference was determined for benign or malignant histopathology results ($P>0.05$).
When all cases with suspected follicular neoplasm, suspected Hürthle-cell neoplasm, suspected malignancy and suspected papillary carcinoma were included into malignancy group, the sensitivity was 79.4%, specificity was 83.8%, overall accuracy rate was 81.8%, positive predictive value was 80.6%, and negative predictive value was 82.7%.
A clinical assessment performed an experienced clinician, US-guided TFNAB performed by an experienced radiologist and pathologic evaluation by a cytopathologist is a team work which will achieve success to identification of malignant thyroid nodules in all patients with nodular thyroid.

DOI: 10.1530/endoabs.37.EP941

EP942

The evaluation of TSH-receptor antibody in hyperthyroid patients treated with surgery or radioactive iodine

Ahmet Dirikoc[1], Fatma Neslihan Cuhaci[1], Husniye Baser[2], Cevdet Aydin[1], Oya Topaloglu[1], Mehmet Kilic[3], Seyda Turkolmez[4], Reyhan Ersoy[1] & Bekir Cakir[1]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Yildirim Beyazit University, Ankara, Turkey; [2]Department of Endocrinology and Metabolism, Ataturk Education and Research Hospital, Ankara, Turkey; [3]Department of General Surgery, Ataturk Education and Research Hospital, Ankara, Turkey; [4]Department of Nuclear Medicine, Ataturk Education and Research Hospital, Ankara, Turkey.

Introduction
Radioactive iodine (RAI) therapy is widely used in the treatment of hyperthyroidism especially in patients with Graves' disease (GD), toxic multinodular goitre (TMNG), and toxic adenoma. RAI may lead to worsening of the autoimmunity with the elevation of TSH-receptor antibody (TRAB). In this study, we aimed to compare the effects of surgery or RAI treatment on TRAB.
Methods
Hyperthyroid patients were divided into three groups; patients in group 1 ($n=23$) had GD conducted to RAI, in group 2 ($n=18$) had TMNG referred to RAI, and group 3 ($n=12$) had GD who underwent to surgery. Before and 12 months after RAI and surgery, sera were collected and analysed for the presence of TRAB.
Results
In group 1, there were eight patients (34.8%) before treatment and 14 patients after treatment with TRAB positivity ($P=0.311$). In group 2, before treatment there were two patients (11.1%) with TRAB positivity, whereas after treatment there were four patients (22.2%) ($P=0.423$). In group 3, TRAB positivity were in six patients (50%) and in one patient (8.3%) before and after treatment respectively ($P=0.296$). However, there was no difference in TRAB positivity between groups 1 and 3 before treatment ($P=0.383$), TRAB positivity was statistically higher in group 1 than group 3 at 12 months of treatment ($P=0.003$). There was no difference between groups 1 and 2 before treatment ($P=0.080$). TRAB positivity was significantly higher in group 1 than group 2 at 12 months of the treatment ($P=0.013$).
Conclusion
RAI treatment can induce autoimmunity in patients with TMNG similar as in patients with GD. We observed similar ratios of TRAB positivity in patients with GD and TMNG before and 12 months after treatment. Whereas 12 months after the treatment, we demonstrated higher TRAB titres in GD patients treated with RAI than underwent to surgery.

DOI: 10.1530/endoabs.37.EP942

EP943

Dynamic thiol/disulfide homeostasis in patients with autoimmune subclinical hypothyroidism

Ihsan Ates[1], Mustafa Altay[1], Fatma Meric Yilmaz[2,3], Canan Topcuoglu[2], Salim Neselioglu[3], Özcan Erel[3] & Nisbet Yilmaz[1]
[1]Department of Internal Medicine, Ankara Numune Education and Research Hospital, Ankara, Turkey; [2]Department of Biochemistry, Ankara Numune Education and Research Hospital, Ankara, Turkey; [3]Department of Biochemistry, Medical Faculty, Yildirim Beyazit University, Ankara, Turkey.

Objective
To investigate dynamic thiol/disulphide homeostasis in autoimmune subclinical hypothyroidism.
Materials and methods
48 patients with newly diagnosed subclinical hypothyroidism due to Hashimoto's thyroiditis and not yet on any treatment and 48 healthy subjects without any known disease were enrolled. Thiol/disulfide homeostasis (native thiol(-SH)–disulphide(-S-S-) exchanges) was measured in both groups with new method developed by Erel and Neselioglu. The half of the difference between total thiol (-SH + -S-S-) and -SH concentrations gave the -S-S- bond amount.
Results
In patients with subclinical hypothyroidism, -SH level and -SH/(-SH + -S-S-) ratio was found to be lower than that of the control group. -S-S- level ($P=0.004$),

-S-S-/-SH ($P=0.001$), and -S-S-/(-SH+-S-S-) ($P=0.001$) ratio was higher in patients with subclinical hypothyroidism as compared to that of the control group. A positive correlation was found between anti-TPO and anti-Tg levels and -S-S-/-SH ve -S-S-/(-SH+-S-S-) levels while a negative correlation was found with -SH/(-SH+-S-S-) level.
Conclusions
Thiol/disulfide homeostasis was found to have a tendency towards -S-S- formation in patients with subclinical hypothyroidism and thyroid autoantibodies were correlated positively with thiol oxidation. Abnormal thiol/disulfide homeostasis in patients with Hashimoto's thyroiditis, is whether a cause or a consequence, may be illustrated by using thiol-containing drugs and following autoantibody levels. The efficacy, dose and duration of thiol drugs may be monitored easily, effectively, quickly and cheaply by the method developed by Erel and Neselioglu.

DOI: 10.1530/endoabs.37.EP943

EP944

Is oxidative stress an effective risk factor in the development of overt hypothyroidism in Hashimoto's thyroiditis?

Ihsan Ates[1], Mustafa Altay[1], Fatma Meric Yilmaz[2], Canan Topcuoglu[2], Nisbet Yilmaz[1] & Serdar Guler[1]
[1]Department of Internal Medicine, Ankara Numune Education and Research Hospital, Ankara, Turkey; [2]Department of Biochemistry, Ankara Numune Education and Research Hospital, Ankara, Turkey; [3]Department of Endocrinology and Metabolism, Ankara Numune Education and Research Hospital, Ankara, Turkey.

Objective
We aimed to investigate the effects of oxidative stress in the pathhogenesis and progression of thyroiditis in patients with Hashimoto's thyroiditis whose aetiopathogenesis includes environmental and genetic factors.
Methods
80 patients (40 euthyroid and 40 subclinical hypothyroidism) older than 18 years with newly diagnosed Hashimoto's thyroiditis and not yet on any treatment were enrolled. Patients were followed up for 9 months. Blood sample was drawn at diagnosis for thyroid function tests and oxidative stress parameters. Total antioxidant status (TAS), total oxidative status (TOS), paraoxonase 1 (PON1), arylesterase, and total thiol (total SH) were measured by colorimetric method. The ratio of serum TOS level and TAS level gave the oxidative stress index. TSH, free thyroxine (fT_4), anti-thyroid peroxidase (anti-TPO), and anti-thyroglobulin (anti-Tg) were measured by ECLIA method.
Results
Total SH level was found to be higher in the euthyroid group as compared to the subclinical hypothyroidism group ($P=0.019$). TAS, TOS, OSI, PON, and arylesterase levels were similar in the two groups ($P>0.05$). At 9 months of follow-up, overt hypothyroidism developed in 14 patients. Patients with overt hypothyroidism tended to have significantly higher average TOS and OSI levels at diagnosis ($P<0.001$) and significantly higher anti-Tg and anti-TPO levels at hypothyroidism development ($P<0.05$) than those who did not develop overt hypothyroidism. Multivariable Cox regression analysis showed TSH level (HR = 1.348, $P<0.001$), fT_4 level (HR = 0.481, $P=0.017$), and OSI ratio (HR = 2.349, $P<0.001$) to be independent predictors for the development of overt hypothyroidism in euthyroid patients and those with subclinical hypothyroidism.
Conclusion
Higher levels of autoantibodies and oxidative stress in patients developing overt hypothyroidism shows that oxidative stress plays a major role in the pathogenesis and progression of autoimmune thyroiditis.

DOI: 10.1530/endoabs.37.EP944

EP945

Does treatment with levothyroxine sodium decrease oxidative stress in Hashimoto's thyroiditis?

Ihsan Ates[1], Mustafa Altay[1], Fatma Meric Yilmaz[2], Nisbet Yilmaz[1] & Serdar Guler[1]
[1]Department of Internal Medicine, Ankara Numune Education and Research Hospital, Ankara, Turkey; [2]Department of Biochemistry, Ankara Numune Education and Research Hospital, Ankara, Turkey; [3]Department of Endocrinology and Metabolism, Ankara Numune Education and Research Hospital, Ankara, Turkey.

Background
In Hashimoto's thyroiditis, chronic inflammation and autoimmunity increases oxidant radicals and cause oxidative stress. However, the effect of levothyroxine therapy on the oxidant and antioxidant systems is not known in overt hypothyroidism. Therefore, we sought to investigate the effect of levothyroxine sodium therapy on oxidative stress in patients with Hashimoto thyroiditis and overt hypothyroidism.
Materials and methods
36 patients (nine males and 27 females) with a diagnosis of Hashimoto's thyroiditis and overt hypothyroidism older than 18 years and not yet on any therapy were enrolled. Blood samples were taken at diagnosis and after 6 months following treatment with levothyroxine for measurements of TSH, free thyroxine (fT_4), anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-Tg), and oxidative stress parameters. TSH, fT_4, anti-TPO, and anti-Tg levels were measured using the ECLIA method. Total antioxidant status (TAS), total oxidative status (TOS), paraoxonase 1 (PON1), aryesterase, and total thiol (total SH) levels were measured using the colorimetric method. Oxidative stress index (OSI) was obtained from the ratio of TOS and TAS levels.
Results
TSH, anti-TPO, and anti-Tg levels decreased after treatment ($P<0.05$) while fT_4 level increased ($P<0.05$). TAS level increased after treatment (1.5 ± 0.2 vs 1.7 ± 0.3, $P=0.030$) while TOS level decreased (6.5 ± 1.9 vs 4.4 ± 1.3, $P=0.012$). OSI ratio also decreased after treatment (4.3 ± 2.3 vs 2.7 ± 1, $P=0.003$). Total SH level increased after treatment (442.8 ± 63.8 vs 470.3 ± 30.1, $P=0.034$), but no significant change was observed in arylesterase and log(PON) levels.
Conclusion
Levothyroxine treatment was found to have positive effects in terms of thyroid antibodies and oxidative stress parameters in patients with Hashimoto's thyroiditis. More studies are needed to understand whether this effect of levothyroxine is due to increase of antioxidant molecules and induction of enzyme synthesis or reduction of inflammation.

DOI: 10.1530/endoabs.37.EP945

EP946

Concomitant Graves' disease and primary hyperparathyroidism: case report

Ramazan Cosar[1], Isilay Kalan Sari[2,3] & Senay Arikan Durmaz[3]
[1]Department of Internal Medicine, Faculty of Medicine, Kirikkale University, Kirikkale, Turkey; [2]Department of Endocrinology and Metabolic Diseases, Burdur State Hospital, Burdur, Turkey; [3]Department of Endocrinology and Metabolic Diseases, Faculty of Medicine, Kirikkale University, Kirikkale, Turkey.

Introduction
Hyperthyroidism is associated with asymptomatic hypercalcaemia due to increased calcium mobilization from bone and catecholamine metabolism. Hypercalcaemia secondary to hyperthyroidism coexist with decreased or normal parathyroid hormone level. We reported case of 30-year-old man who suffered from Graves' disease and primary hyperparathyroidism.
Case report
A 30-year-old male patient was admitted to our hospital suffered from palpitation, heat intolerance and sweating. He had blood pressure of 130/90 mmHg, heart rate of 102 beats/min, and temperature of 36.6 °C. He had warm and moist skin. Blood tests showed TSH <0.03 μU/l, fT_3 14.34 pg/ml, and fT_4 3.91 pg/ml. Other results: anti-TPO 229 IU/ml, TRAbs 0.73 U/l, serum calcium 11.05 mg/dl, inorganic phosphorus 3.61 mg/dl, iPTH 85.9 pg/ml, and 25-OH vitamin D_3 31.8 ng/ml. The 24-h collected urine showed creatinine clearance of 132 ml/min and calcium excretion of 428 mg/day. Other laboratory parameters were largely within normal ranges. Ultrasonography revealed enlarged thyroid gland with inhomogeneous pattern. Scintigraphy of the thyroid gland was consistent with Graves' disease. Scintigraphy of the parathyroid glands revealed parathyroid adenoma. Patient was treated with propylthiouracil 300 mg/day and propranolol 20 mg twice a day. Treatment successfully controlled sympathetic symptoms. When he became euthyroid, serum calcium, and parathyroid hormone was still elevated. Subtotal thyroidectomy and parathyroidectomy was performed. The follow-up investigations showed normalisation of serum calcium and parathyroid hormone.
Conclusion
Constant hypercalcemia after treatment of hyperthyroidism may indicate concomitant hyperparathyroidism if iPTH level is not reduced. It should be considered that; slightly or moderately elevated iPTH levels in hypercalcaemia coexists with hyperthyroidism, may suggest hyperparathyroidism. Ultrasonography, scintigraphy, and ultrasound guided fine-needle biopsy of parathyroid

gland lesions can be used for differential diagnosis. Avoiding from repeated operations and complications; the best treatment is combined resection of thyroid and parathyroid gland when concomitant parathyroid adenoma is determined.

DOI: 10.1530/endoabs.37.EP946

EP947

Measurement of epicardial adipose tissue (EAT) thickness in subclinical hypothyroid patients and to determine the relationship between EAT and abdominal/visceral fat mass

Dilek Arpaci[1], Aysel Gurkan Tocoglu[1], Sabiye Yilmaz[2], Sumeyye Korkmaz[1], Hasan Ergenc[1], Huseyin Gunduz[2], Nurgul Keser[2] & Ali Tamer[1]
[1]Department of Internal Medicine, Sakarya Education and Research Hospital, Sakarya University, Sakarya, Turkey; [2]Department of Cardiology, Sakarya Education and Research Hospital, Sakarya University, Sakarya, Turkey.

Background
Subclinical hypothyroidism (SH) is defined as high TSH accompanied with normal free thyroxine (FT_4). SH has found to be associated with cardiovascular disease (CVD) and increased mortality. Epicardial adipose tissue (EAT) is now considered to be a new noninvasive measurement method used for the early detection of CVD susceptibility. EAT has vasocrine and paracrine actions which lead to CVD. We aimed to evaluate measurement of EAT and to detect relationship between EAT and abdominal/visceral fat mass in patients with SH.
Material and methods
This study included 41 patients with SH and 35 healthy controls (matched in age and gender). Demographic data (age, gender, BMI, fat mass (FM), abdominal FM, visceral FM, waist circumstance (WC), hip circumstances (HC), systolic and diastolic blood pressure) and laboratory results (fasting plasma glucose (FPG), LDL cholesterol (LDL-c), HDL cholesterol (HDL-C), triglycerides (TGs), FT_4, TSH, and anti-TPO) were recorded. EAT was measured with transthoracic echocardiography.
Results
Fat mass, BMI, WC, and WC/HC ratio, visceral and abdominal fat mass were higher in the study group than the control group ($P<0.05$). While there were no differences in terms of FPG ($P=0.780$), there were significant differences regarding LDL-C and TGs between the two groups ($P=0.002$ and $P=0.026$ respectively). Serum TSH and anti-TPO levels were found higher and FT_4 level was lower in the study group than the control group ($P<0.05$). Although, there were significant differences in terms of BMI, FM, abdominal and visceral FM, WC, HC, WC/HC ratio, LDL-C, and TG, there were no differences in EAT between the two groups. Mean EAT was 4.61 ± 0.06 mm in the study group and 4.51 ± 0.07 mm in the control group ($P=0.532$). While positive correlation was found between EAT and demographic parameters and serum TG levels ($P<0.05$), no correlation was found between EAT and TSH, FT_4, LDL-C, and anti-TPO level ($P>0.05$).
Conclusion
Despite EAT has been playing an important role in predicting subclinical atherosclerosis in SH, this study could not support this. In our opinion, more studies with more number of patients are needed to claim that.

DOI: 10.1530/endoabs.37.EP947

EP948

High circulating levels of SICAM-1 and SVCAM-1 in patients with Hashimoto's thyroiditis

Aysenur Ozderya[1], Kadriye Aydin[1], Sule Temizkan[1], Semra Dogru Abbasoglu[2], Pervin Vural[2] & Yuksel Altuntas[3]
[1]Department of Endocrinology and Metabolism, Kartal Dr Lutfi Kirdar Training and Research Hospital, Istanbul, Turkey; [2]Department of Biochemistry, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey; [3]Department of Endocrinology and Metabolism, Sisli Etfal Training and Research Hospital, Istanbul, Turkey.

Objective
Elevated levels of the soluble adhesion molecules, sICAM-1 and sVCAM-1 reflect chronic inflammatory state. Increased levels of sICAM-1 and sVCAM-1 were demonstrated in various autoimmune thyroid diseases with abnormal thyroid function, but their clinical significance is undefined, especially in the euthyroid patients with Hashimoto's thyroiditis (HT). Increased levels of soluble adhesion molecules are also associated with components of the metabolic syndrome like diabetes mellitus, insulin resistance and obesity, and beyond thyroid dysfunction, HT is believed to affect metabolic parameters. Accordingly, in the present study we aimed to analyze sICAM-1 and sVCAM-1 levels in HT, their relation with thyroid autoimmunity and glucose metabolism markers in HT.
Methods
Eighty euthyroid patients with HT, and age- and BMI-matched 80 control participants were enrolled. Serum sICAM-1, sVCAM-1, free triiodothyronine (fT_3), free thyroxine (fT_4), TSH, thyroid peroxidase antibody (anti-TPO), thyroglubulin antibody (anti-TG), fasting blood glucose, insulin, lipid levels, and homeostatis model assessment for insulin resistance (HOMA-IR) were assessed in all participants.
Results
Patients with HT had significantly higher levels of sICAM-1 and sVCAM-1 than controls (both $P<0.001$) as well as glucose metabolism parameters. Correlation analysis revealed that both sICAM-1 and sVCAM-1 were significantly positively correlated with TSH, glucose, anti-TG, and anti-TPO; while sVCAM-1 was correlated with fasting insulin, HOMA-IR, HDL-C positively and with TG negatively in whole study group. However, these relations were not present when patients and controls were analyzed separately. Regression analysis demonstrated that sICAM-1 was related with anti-TPO and sVCAM-1 was related with both anti-TPO and anti-TG.
Conclusion
sICAM-1 and sVCAM-1 levels were significantly elevated in HT and correlated closely with thyroid autoimmunity. Moreover, soluble adhesion molecules, specifically sVCAM-1 had a strong relation with metabolic parameters in HT.

DOI: 10.1530/endoabs.37.EP948

EP949

Elevated neutrophil/lymphocyte ratio in patients receiving any replacement therapy with euthyroid Hashimoto

Havva Keskin[1], Yasemin Kaya[4], Kenan Cadirci[2], Cuneyt Kucur[5], Elif Ziypak[2], Eda Simsek[2], Hakan Gozcu[2], Senay Arikan[3] & Ayse Carlioglu[2]
[1]Medeniyet University, Istanbul, Turkey; [2]Erzurum Training and Research Hospital, Erzurum, Turkey; [3]Kirikkale University, Kirikkale, Turkey; [4]Ordu University, Ordu, Turkey; [5]Dumlupinar University, Kutahya, Turkey.

Introduction
Neutrophil lymphocyte rate (NLO), which is obtained from peripheric blood and used as mathematical rates of lymphocyte numbers, is accepted as available and practical indicator of systemic inflammation existence. We aimed to search NLO between Hashimoto's thyroids patients who have autoimmune thyroid and also include an aetiopathogenesis auto-inflammatory process, and healthy control group with this study.
Method
59 patients who have been diagnosed as Hashimoto's thyroiditis, euthyroid and receive any treatment, 53 people who have no in point of age, BMI among them, totally 112 people have been incorporated to the study. The average age of patients has been counted as 33.8 ± 12.8 years and the average age of control group has been counted as 30.1 ± 12.4 years. Statistically significant difference couldn't be determined ($P=0.1$).
Results
As a result of this study; patient group NLO has been founded as 4.0 ± 0.7 and healthy group NLO has been founded as 2.0 ± 0.1. Statistically significant difference has been determined ($P=0.01$). While statistically significant difference hasn't been determined between healthy group and patient group in point of white blood cell count (7.9 ± 0.3 and 7.4 ± 0.2, $P=0.1$) among neutrophil (5.5 ± 0.3 and 5.4 ± 1.1, $P=0.9$), the difference has been determined in point of lymphocyte values (2.04 ± 0.1 and 3.1 ± 0.5, $P=0.05$). Positive correlation has been determined between NLO and CRP ($r=0.6$, $P<0.0001$), thyroid peroxidase immune body level and ($r=0.3$, $P<0.001$), anti-thyroglobulin immune body level and ($r=0.3$, $P=0.006$), white blood cell count and ($r=0.4$, $P<0.001$) and also between neutrophil level and NLO ($r=0.265$, $P=0.007$), neutrophil and lymphocyte count ($r=0.776$, $P<0.001$).

Discussion
Present symptoms show that NLO values have statistically significant increased in euthyroid Hashimoto's thyroiditis in comparison with healthy control group and it is seen that it correlated with autoantibody level which is used for the diagnosis of disease. In these results, we think that systemic inflammatory process is important in Hashimoto's thyroiditis aetiology.

DOI: 10.1530/endoabs.37.EP949

EP950

Radioiodine treatment of Graves' disease: dose–response analysis

Jitka Cepkova, Ioannis Svilias, Eva Krcalova & Jiri Horacek
University Hospital Hradec Kralove, Charles University in Prague, Hradec Kralove, Czech Republic.

Introduction
Despite more than 60 years' experience with radioactive iodine ^{131}I (RAI) treatment of Graves' disease (GD) about the most appropriate dosing regime is still controversial. The objective of our research was to analyse the outcome of RAI therapy in our cohort of patients.
Methods
Retrospectively, we analysed 603 patients with GD (500 women and 103 men, mean age 51.5 ± 12.7 years) treated with RAI. According to recommended practice in Czech Republic, most patients came with at least 1-year history of the disease, in the first or next relapse. Their antithyroid medication was withdrawn 3–4 days before RAI administration. The treatment was considered successful if patients were euthyroid or hypothyroid on follow-up.
Results
Total efficacy of RAI treatment was 74% in 6 months and 88% in 12 months. We divided our cohort into three subgroups according the adjusted dose (adjusted to thyroid volume and 24-h RAI accumulation): i) in the first group ($n=120$) with adjusted dose 0.5–5.0 MBq/g the success rate was 54% in 6 months and 72% in 12 months, ii) in the second group ($n=239$) with adjusted dose 5.1–8.4 MBq/g it was 71 and 86%, and iii) in the third group ($n=244$) with adjusted dose 8.5–77.2 MBq/g it was 86 and 96% respectively. Median adjusted dose in the second group was 6.8 MBq/g. In the detailed analysis of the third group, any further dose increase over 8.5 MBq/g did not result in higher cure rates. In patients with higher thyroid volume ($P<0.001$) and higher disease activity (i.e. higher fT_3, fT_4, TSHR-Ab, and 24-h RAI accumulation as well as suppressed TSH), there was an increased risk of treatment failure. The therapy efficacy was not dependent on sex ($P=0.580$) and age ($P=0.578$).
Conclusion
With adjusted dose of 8.5 MBq/g, very reasonable efficacy was attained. In patients with smaller gland and lower disease activity it was possible to administer lower adjusted dose, ~6.5–7 MBq/g.

DOI: 10.1530/endoabs.37.EP950

EP951

Serum H-FABP levels in patients with overt hypothyroidism

Esra Tutal[1], Mustafa Ozbek[1], Muyesser Sayki Arslan[1], Oya Topaloglu[1], Taner Demirci[1], Melia Karakose[1], Mustafa Caliskan[1], Ilknur Ozturk Unsal[1], Askin Gungunes[1], Evrim Cakir[1], Bekir Ucan[1], Nujen Colak Bozkurt[1], Gulfer Ozturk[2], Mustafa Sahin[3], Erman Cakal[1] & Tuncay Delibasi[1,4]
[1]Department of Endocrinology and Metabolism, Diskapi Teaching and Research Hospital, Ankara, Turkey; [2]Department of Biochemistry, Diskapi Teaching and Research Hospital, Ankara, Turkey; [3]Department of Endocrinology and Metabolism, School of Medicine, Ankara University, Ankara, Turkey; [4]Department of Internal Medicine, School of Medicine (Kastamonu), Hacettepe University, Ankara, Turkey.

Aim
Overt hypothyroidism affects mostly women with an increased prevalence in individuals by age. Hypothyroidism is associated with accelerated atherosclerotic cardiovascular diseases, possibly caused by the higher incidence of hyperlipidemia, insulin resistance, hypertension which all are associated to hypothyroidism. Heart-type fatty acid binding protein (H-FABP) is specific for cardiomyocytes and a sensitive marker of myocardial injury. The purpose of this study is examining the effect of hypothyroidism on H-FABP levels and carotid artery intima–media thickness (CIMT) level.
Methods
We measured serum H-FABP levels in 33 patients with overt hypothyroidism and age, gender, and BMI-matched 39 control subjects. All participants underwent high-resolution B-mode ultrasonography in order to measure CIMT.
Results
Serum levels of H-FABP were not found significantly different in the patient group in comparison with the controls (1515.87 ± 2143 pg/ml vs 953 ± 416 pg/ml, $P=0.15$ respectively). CIMT was significantly higher in the patient group than in the control group (0.53 ± 0.08 mm vs 0.48 ± 0.05 mm, $P<0.05$). However, the HOMA-IR and fasting insulin levels did not differ between the two groups ($P>0.05$).
Conclusion
Based on the results of this study, H-FABP seems not a useful marker while detecting preclinical atherosclerosis in patients with overt hypothyroidism but CIMT might be useful to detect early atherosclerosis.

DOI: 10.1530/endoabs.37.EP951

EP952

Evaluation of geriatric patients with hyperthyroidism treated with radioactive iodine-131

Umut Elboga[1], Mesut Ozkaya[2], Mustafa Basibuyuk[1], Ayten Eraydin[2] & Y Zeki Celen[1]
[1]Department of Nuclear Medicine, Gaziantep University, Gaziantep, Turkey; [2]Department of Endocrinology, Gaziantep University, Gaziantep, Turkey.

Introduction
In this study, we aimed to evaluate radioiodine (RAI) treatment efficacy in geriatric patients with hyperthyroidism.
Design
Patients older than 65 years who received RAI treatment were included via retrospective data analyses. Eighty-two patients with hyperthyroidism (average age: 69.9 years, age range: 64–81 years) who received RAI treatment and then followed up for at least 6 months were included in the study. Patients' clinical and laboratory results were analysed retrospectively. Euthyroid or hypothyroid status at the end of the year after treatment was deemed to be a response to treatment.
Results
Nineteen patients were men (average age: 68.3 years, age range: 64–75 years), the 63 were women (average age: 71.3 years, age range: 65–81 years). According to thyroid ultrasound or physical examination findings, 13 patients had diffuse thyroid hyperplasia, the other patients had non diffuse hyperplasia (nodular or multinodular). RAI treatment was given to the patients once or twice, or three times if necessary. In first RAI treatment, average 12.7 mCi, in second, average 15.1 mCi, and in third, average 20.7 mCi were given orally. 41 (50%) patients were euthyroid, 19 (23.1%) were hypothyroid, and 22 (26.9%) were thyrotoxic. Success rate of RAI treatment was 73.1%. The highest success rate was obtained in geriatric patients who have diffuse thyroid hyperplasia. Serious side-effects were not observed in our patients.
Conclusion
We observed approximately similar success rates with the reported results in RAI treatment of geriatric patients with hyperthyroidism and also side effects of RAI treatment were low. We believe that RAI treatment should be first choice for treatment of hyperthyroidism in geriatric patients, because it is easy to perform and its side effects are very low.

DOI: 10.1530/endoabs.37.EP952

EP953

Safety and efficacy of rapid thyroid blockade with Lugol's iodine in the pre-surgical management of Graves' thyrotoxicosis

Azmi Mohammed, W Elsaify, Rasha Mukhtar & Sath Nag
The James Cook University Hospital, Middlesbrough, UK.

Introduction
A significant number of patients are intolerant of anti-thyroid drugs (ATD) and thyroidectomy remains the only treatment option available to patients who decline radioiodine as definitive therapy. As patients with poorly controlled thyrotoxicosis are at risk of developing thyroid storm, optimal pre-operative control of hyperthyroidism is essential. Rapid thyroid blockade (RTB) with the contrast agents sodium ipodate and iopanoic acid were attractive treatment options but these agents are no longer available for routine use.
Aims
To explore the safety and efficacy of rapid thyroid blockade with Lugol's iodine in the pre-surgical management of Graves' thyrotoxicosis.
Method
Lugol's iodine (0.2 ml three times a day) was administered to six patients with Graves' thyrotoxicosis who were resistant to treatment with the conventional ATD, carbimazole, and propylthiouracil. Treatment was started 10 days prior to planned thyroid surgery. TSH at baseline and subsequent fT_4 and fT_3 were measured at fixed intervals prior to thyroidectomy.
Results
All patients were female; mean (S.D.) pre-treatment fT_4 and fT_3 levels were 30.1 pmol/l (8.12) and 8.8 pmol/l (5.9) respectively. Mean nadir fT_4 and fT_3 levels after treatment were 16.2 and 4.4 pmol/l respectively. Mean percentage fT_4 reduction was 45.2% and mean percentage fT_3 reduction was 40.4%. fT_4 and fT_3 dropped at an average rate of 7.6 pmol/l per day. Mean absolute reductions in fT_4 and fT_3 levels were13.9 and 4.4 pmol/l respectively. All patients were biochemically euthyroid preoperatively. The mean time to normalise fT_4 was 3.8 days (S.D. 1.72). On patient experienced transient adverse effects with Lugol's iodine.
Conclusion
In this pilot study, Lugol's iodine was effective in rendering patients biochemically euthyroid prior to planned thyroidectomy. The long-term safety and efficacy of crash thyroid blockade with Lugol's iodine needs to be assessed in a larger cohort of patients.

DOI: 10.1530/endoabs.37.EP953

EP954

Higher titre of TSH receptor antibody was associated with better responsiveness of thyroid hormone to antithyroidal drug in Graves' disease

Hoonsung Choi[1] & Won Sang Yoo[2]
[1]Department of Internal Medicine, Kangwon National University Hospital, Chuncheon-si, Republic of Korea; [2]Department of Internal Medicine, Dankook University Hospital, Cheonan-si, Republic of Korea.

Introduction
Antithyroidal drug (ATD) therapy is considered as choice of treatment for Graves' disease; however, the response of treatment varied between patients. Although several studies reported risk factors for relapse after initial treatment, there were few studies for the responsiveness during early treatment period.
Method and design
We reviewed 94 patients with Graves' disease and used their initial TSH receptor antibody (TSHRAb) titre and consequent free T4 levels during follow up periods. Drug responsiveness was defined as the correlation coefficients between decreasing rates of free T4 levels and exposed dose of ATD. We analysed and compared the coefficients of each patient according to clinical characteristics and TSHRAb titre.
Results
The mean age of subjects was 47.1 ± 15.4 years old and male patients were 26 (28%). The mean titre of initial TSHRAb was 19.1 ± 14.0 IU/L. Although the correlation coefficients did not showed significant association with age group (≤ 40, $41 \sim 60$, $60 <$) and sex, higher titre of TSHRAb was associated with better responsiveness (-0.13 ± 0.10 vs. -0.16 ± 0.16 vs. -0.22 ± 0.13, respectively in three groups (≤ 10, $10.1 \sim 20$, $20 <$)). We could also observe significant correlation between the consequent TSHRAb titre and the responsiveness.
Conclusion
Our results suggest the possible usage of TSHRAb titre to decide the optimal initial ATD dose and its adjustment in early treatment periods.

DOI: 10.1530/endoabs.37.EP954

EP955

Shear-wave elastography in diagnostics of primary hyperparathyroidism – new application of the method

Adam Stangierski, Kosma Wolinski, Ewelina Szczepanek-Parulska & Marek Ruchala
Department of Endocrinology, Metabolism and Internal MedicinePoznan University of Medical Sciences, Poznan, Poland.

Introduction
Shear wave elastography (SWE) is a reliable, objective and reproducible technique in sonographic assessment of tissue stiffness. It is considered to be an improvement of conventional ultrasonographic examination. It was demonstrated to be useful in the diagnosis of many thyroid disorders, such as thyroid cancer, Hashimoto's thyroiditis or Graves' disease. The aim of our study was to check if SWE can be supportive in the diagnosis of primary hyperparathyroidism.
Materials and methods
43 patients referred for the surgery due to primary hyperparathyroidism were included. In all cases presence of parathyroid adenoma was confirmed by histopathology. Control group consisted of 322 benign thyroid nodules in 98 patients referred for surgery. Maximal elasticity (E_{max}) of each lesion was recorded.
Results
Mean E_{max} value for parathyroid adenomas was 14.4 kPa with S.D. 17.1 kPa; median was 11.1 kPa. For benign thyroid lesions mean E_{max} was equal to 57.3 with S.D. = 60.6, median = 36.2 kPa. The difference was statistically significant ($P =$). E_{max} of the parathyroid adenomas was inversely correlated with PTH level ($P = 0.04$, $r = -0.32$).
Conclusions
Parathyroid adenomas turned out to be significantly and distinctly more elastic than benign thyroid lesions – median values of the stiffness differed over three times. SWE can be a useful supportive method in the diagnosis of such lesions. Presence of very soft lesions, localised typically near the rear wall of the thyroid may arouse suspicion of primary hyperparathyroidism and hinting further diagnostic, such as measurement of PTH, calcium and phosphate serum concentrations.

DOI: 10.1530/endoabs.37.EP955

EP956

The role of antithyroglobulin, antiperoxidase and anti-TSH autoantibodies in amiodarone induced thyrotoxicosis or amiodarone induced hypothyroidism (a two-center study)

Agata Czarnywojtek[1,2], Malgorzata Zgorzalewicz-Stachowiak[3], Marta Fichna[1], Kosma Wolinski[1], Maria Teresa Plazinska[4], Adam Stangierski[1], Pawel Gut[1], Izabela Miechowicz[5], Hanna Komarowska[1], Rafal Czepczynski[1], Leszek Krolicki[4] & Marek Ruchala[1]
[1]Department of Endocrinology, Metaboilsm and Internal Medicine, Poznan University of Medical Sciences, Poznan, Poland; [2]Department of Pharmacology, Poznan University of Medical Sciences, Poznan, Poland; [3]Department of Health Prophylaxis, Laboratory of Medical Electrodiagnostics, Poznan University of Medical Sciences, Poznan, Poland; [4]Nuclear Medicine Department, Medical University of Warsaw, Warsaw, Poland; [5]Department of Computer Science and Statistic, Poznan University of Medical Sciences, Poznan, Poland.

Purpose
In the recent study it has been reported, that elevated serum concentrations of TSH receptor (TSH-R), antithyroglobulin (Tg), antiperoxidase (TPO) autoantbodies (Abs) may be observed in the subjects treated for amiodarone induced thyrotixicosis (AIT) type I, decreased in type II of AIT, or changed in amiodarone induced hypothyroidism (AIH). This study was done to analyse the changes of Tg-Abs, TPO-Abs and TSH-R-Abs titer in euthyroid, hyperthyroid (AIT), and hypothyroid (AIH) patients.
Methods
The study consisted of 217 patients diagnosed in the Chair and Department of Endocrinology, Metabolism and Internal Medicine, Poznan, and 63 patients treated in the Department of Nuclear Medicine, in Warsaw, Poland between January 2003 and December 2014. Titer of serum TPO-Abs, Tg-Abs, TSH-R-Abs were analyzed retrospectively, in euthyroid patients with the history of hyperthyroidism prior to re-administration of amiodarone (group A), patients with AIT who discontinued AM therapy (group B), patients with AIT chronically treated with AM (group C), and hypothyroid patients (AIH, group D).

Results
Statistically significant differences were observed in serum Tg-Abs values between groups: A and B ($P=0.001$), A and D ($P=0.001$), B and D ($P=0.01$), A and C ($P=0.001$), B and C ($P=0.001$). In case of serum level of TPO-Abs, we found statistically significant differences between groups: A and C ($P=0.05$), B and C ($P=0.001$), C and D ($P<0.05$). Serum TSH-R-Abs were not elevated in any of the studied groups, and the titers did not differ between patients with AIT and AIH. TPO-Abs and Tg-Abs were in normal ranges in all groups.
Conclusion
Normal or slightly decreased titer of TPO-Abs, Tg-Abs, TSH-R-Abs were observed in all studied groups. Observed statistically significant differences were not clinically relevant. Discontinuing or continuing amiodarone therapy had no influence on the titer of autoantibodies.

DOI: 10.1530/endoabs.37.EP956

EP957

Rho/Rho-kinase gene expressions in Graves' disease and Hashimoto's thyroiditis

Suzan Tabur[1], Serdar Oztuzcu[1], Elif Oguz[2], Mesut Ozkaya[1] & Abdullah Tuncay Demiryurek[1]
[1]Gaziantep University, Gaziantep/Sahinbey, Turkey; [2]Harran University, Sanliurfa/Yenisehir, Turkey.

Introduction
Autoimmune thyroid diseases result from a dysregulation of the immune system leading to an immune attack on the thyroid. Autoimmune thyroid diseases, which include Graves' disease (GD) and Hashimoto's thyroiditis (HT), are characterised by lymphocytic infiltration of the thyroid parenchyma. The mechanisms that trigger the autoimmune attack to the thyroid are not entirely known. The aim of this study was to investigate the possible contribution of Rho/Rho-kinase gene expressions in GD and HT.
Methods
A total of 47 patients with GD, 41 patients with HT, and 42 healthy control subjects with similar age and sex were included to this study. mRNA from blood samples was extracted, and real time polymerase chain reaction on the BioMark HD dynamic array system (Fluidigm, South San Francisco, CA) was performed for the Rho/Rho-kinase gene expressions. For calculation of the significance of differences in gene expressions, the Mann–Whitney *U*-test was used.
Results
Gene expression analysis showed that RHOC, RHOF, RAC1, and ROCK1 mRNA contents in leukocytes were markedly depressed, and RHOH gene was up-regulated in both GD and HT patients when compared to the control groups ($P<0.05$). Although CDC42 gene expression was decreased in GD, it was augmented in HT. Additionally, RHOQ, RHOU, RHOV, RHOBTB1, RHOBTB3, and RAC3 expressions were significantly suppressed in HT ($P<0.05$). There was also decrease in ROCK2 gene expression in HT ($P<0.05$). No marked changes were noted in RHOA, RHOB, RHOD, and RND3 (RHOE) genes in GD and HT groups.
Conclusion
In conclusion, to the best of our knowledge, these results are the first to demonstrate the contribution Rho/ROCK gene expressions in GD and HT. Our data showed that these gene expressions may contribute to the pathology of GD and HT.
Disclosure
This study was supported by a project (SBAG 213S021) from the TUBITAK, Ankara, Turkey.

DOI: 10.1530/endoabs.37.EP957

EP958

Survey on the steroid dose for patients with subacute thyroiditis in a Korean tertiary hospital

Won Jun Kim[1], Sangmo Hong[2], Myoung Sook Shim[1] & Jin Yeob Kim[1]
[1]Department of Endocrinology and Metabolism, University of Ulsan College of Medicine, Gangneung Asan Hospital, Gangneung, Republic of Korea; [2]Department of Endocrinology and Metabolism, University of Hanyang College of Medicine, Hanyang Guri Hospital, Guri, Republic of Korea.

Introduction
Subacute thyroiditis (SAT) is most common cause of painful thyroiditis. Although prednisolone at 40 mg/d has been preferred as initial dose for moderate to severe SAT, there have also been other recommendations as 25–60 mg/day in many reports. We retrospectively assessed the effect of steroid dose on the SAT.
Methods
We examined 132 patients with SAT who visited our endocrinology clinic at least three times between January 2005 and December 2012. We excluded patients without high ESR level, steroid prescription, and follow-up within 6month after resolution. Final number of subjects was 63. The outcome in the group with initial steroid dose less than 30 mg ($n=22$, 34.9%) was compared with that with 30 mg or more ($n=41$, 65.1%).
Results
The mean age of the total patients was 48.2 years. The incidence was most prevalent from September to November (40%, $n=26$). The mean of initial prednisolone dose was 30.2 mg, while tapering steroid dosage for the mean duration of 7.6 weeks. Six patients (9.5%) have relapsed within 6 months. The clinical outcome in the group with less dosage was not significantly different from that in the group with more dosage, such as total administration period ($P=0.804$), the recurrence rate ($P=0.423$), TSH ($P=0.826$), free T4 ($P=0.072$), ESR ($P=0.079$), 99 m-Technisium thyroid scan uptake ($P=0.185$). Although no serious side effect was observed, three cases of epigastric discomfort and swelling was reported in higher dosage group.
Conclusion
In our study, the initial dosage for the treatment of SAT with less than 30mg appeared as effective as 30 mg or more. Relapse of SAT seemed not dependent on the initial dose of prednisolone.

DOI: 10.1530/endoabs.37.EP958

EP959

Difficulties in the interpretation of urinary iodine excretion in pregnant women

Zsuzsanna Szanto[1,2], Attila Csiszer[3], Zsuzsanna Croitorescu[4] & Imre Zoltan Kun[5]
[1]Department of Endocrinology, University of Medicine and Pharmacy, Tirgu-Mures, Romania; [2]Clinical Department of Endocrinology, Clinical Hospital Mures County, Tirgu-Mures, Romania; [3]Regional Center of Public Health, National Institute of Public Health, Tirgu-Mures, Romania; [4]Central Laboratory, Clinical Hospital Mures County, Tirgu-Mures, Romania; [5]Doctoral School, University of Medicine and Pharmacy, Tirgu-Mures, Romania.

Introduction
The urinary iodine excretion (UIE) from fasting morning urine sample is a good epidemiologic indicator for iodine state, used in populational groups (school-children, pregnant women) at risk to develop iodine deficiency disorders. It is not adequate to evaluate individual iodine intake. In pregnant women, especially with chronic autoimmune thyroiditis, it is important to estimate iodine state.
Objectives
To evaluate the individual iodine state in pregnant women comparing UIE from morning and 24-hours urine samples.
Material and methods
24-h UIE was determined in 23 pregnant women, and the values expressed in μg/l and μg/g-creatinine were compared to each other. Morning UIE was additionally assessed in 11 women, and compared to the 24-hours UIE levels.
Results
The mean 24-hours UIE was 157.64 ± 69.50 μg/l, with 44% lower than 273.53 ± 121.76 μg/g-creatinine ($P=0.0003$, 95% CI=56.96–174.80). The individual values expressed in μg/l and μg/g-creatinine were in concordance in most of the cases (87%), both being normal or both being reduced. In three women (13%) the 24-hours UIE in μg/l suggested iodine deficiency, while the values in μg/g-creatinine indicated normal iodine intake. In the 11 pregnant women the mean morning UIE was 155.36 ± 75.87 μg/l, similar with the 24-hours UIE μg/l (156.7 ± 60.69), but with 30.4% lower than the 24-hours UIE μg/g-creatinine (225.29 ± 86.74, $P=0.0578$). In nine cases (81.8%) all the three UIE values (morning UIE, 24-hours UIE μg/l, 24-hours UIE μg/g-creatinine) indicated concordantly iodine deficiency or normal iodine intake, in the other two (18.2%) the different UIE suggested different iodine state.
Conclusions
Important differences were observed between the morning UIE, 24-hours UIE in μg/l, 24-hours UIE in μg/g-creatinine, however the interpretation of these were mostly in concordance (87%). In 13% the results could not clearly show iodine

state. Project no. 34/2013 financially supported by the internal research grants from the University of Medicine and Pharmacy Tirgu-Mures, Romania.
Disclosure
This work was supported by the Internal Research Grants of University of Medicine and Pharmacy Tirgu Mures, Romania (grant number 34/2013).
DOI: 10.1530/endoabs.37.EP959

EP960

Surgical and pathological changes after radiofrequency ablation of thyroid nodules

Chiara Dobrinja[1], Stella Bernardi[2], Bruno Fabris[2], Rita Eramo[1], Petra Makovac[1], Gabriele Bazzocchi[3], Fabrizio Zanconati[2] & Fulvio Stacul[3]
[1]General Surgery, Cattinara Teaching Hospital, Trieste, Italy; [2]Department of Medical, Surgical, and Health Sciences, University of Trieste, Trieste, Italy; [3]Radiology Unit, Maggiore Hospital, Trieste, Italy.

Background
Radiofrequency ablation (RFA) is an effective technique for the treatment of symptomatic benign thyroid nodules. It is not known to what extent RFA may affect thyroid surgery and/or histological diagnosis.
Materials and methods
patients were treated with RFA and then followed for 2 years. RFA was performed on 64 symptomatic Thy2 nodules and on six symptomatic Thy3 nodules, without atypical cells nor BRAF or NRAS mutations, in surgically high-risk individuals or patients unwilling to undergo surgery. Volume reduction was evaluated at 1, 3, 6, 12, and 24 months after the procedure. Two Thy3 nodules regrew after the procedure, and the patients accepted to undergo a total thyroidectomy. Here we present how RFA has affected their operation or the final pathology of the surgically removed nodules.
Results and conclusions
RFA is effective for the treatment of Thy2 nodules. RFA should not be used for the treatment of Thy3 nodules, as it only delays surgery in case of malignancy. One session of RFA does not affect subsequent thyroid surgery and/or histological diagnosis.
DOI: 10.1530/endoabs.37.EP960

EP961

Serum total sialic acid levels in overt and subclinical hypothyroid patients and its relationship with atherosclerotic risk factors

Mustafa Altay[1], Mehmet Ayhan Karakoç[1], Nuri Çakır[1], Etem Turgay Cerit[1], Müjde Aktürk[1], Canan Yılmaz Demirtaş[2], Neslihan Bukan[2] & Metin Arslan[1]
[1]Gazi University Medical Faculty, Department of Endocrinology and Metabolism, Ankara, Turkey; [2]Gazi University Medical Faculty, Clinical Biochemistry, Ankara, Turkey.

Objective
Serum total sialic acid(SA) concentration is assessed as an up to date risk indicator of atherosclerosis and cardiovascular diseases.
Methods
It was aimed to investigate about how SA levels are effected in overt or subclinical hypothyroidism (SH) and how it's associated with other atherosclerosis risk factors because there is no study about these topics, though SA is intensively studied in recent years.
Patients
Sixty newly diagnosed treatment-naive hypothyroid patients (35 subclinical and 25 overt) and 30 euthyroid individuals were included in the study. Fasting blood samples were taken and SA, serum homocystein and hsCRP was measured in addition to routine biochemical measurements and carotid artery intima media thickness (CIMT) measurements were performed.
Results
Diastolic blood pressure, CIMT, Total-C, LDL-C, TG levels were significantly increased in patients. Other atherogenesis related measurements such as systolic blood pressure, uric acid, hsCRP and homocystein levels were also increased in patients, but not statistically significant. Serum total SA levels were higher in hypotyroid patients compared to controls but the difference was not statistically significant. In patients' group positive correlation between CIMT and SA was determined as it was between SA and uric acid.
Conclusions
Interesting result of our study is the positive relationship between SA and CIMT which is revealed for the first time. The existence of correlation between SA and some indicators like CIMT, hsCRP and uric acid in hypothyroid group suggests that it can be an atherogenesis indicator in hypotyroid patients.
DOI: 10.1530/endoabs.37.EP961

EP962

Lifestyle intervention reduces TPO antibody level in euthyroid patients: a retrospective cohort study

Liang Chen, Jian Kuang, Jianhao Pei, Hongmei Chen, Zhong Chen, Zhongwen Li, Huazhang Yang, Xiaoyin Fu, Long Wang & Zhijiang Chen
The First Division of Endocrinology, Guangdong Academy of Medical Sciences, Guangdong General Hospital, Guangzhou, China.

Objective
To investigate the impact of lifestyle intervention on elevated thyroid peroxidase (TPO) antibody levels in outpatients with normal thyroid function.
Methods
A retrospective cohort study was performed to observe and evaluate euthyroid patients with excessive TPO antibodies that presented to the authors' hospital between March 2013 and October 2014 for routine medical examinations. The subjects were randomly divided into the lifestyle intervention group and the control group. Lifestyle interventions, including diet improvement and adequate sleep, were instituted immediately following the medical examination for 12–24 weeks. Both groups had patients taking either selenium supplements or Chinese herbal medicines. The difference between the two groups in TPO antibody level was compared after lifestyle intervention.
Results
The TPO antibody level decreased by 30% in the intervention group and only 5% in the control group ($P<0.05$).
Conclusion
Increased TPO antibody level is often related to autoimmune thyroid disorders and inflammation, including conditions such as toxic goitre or autoimmune thyroiditis. The present cohort study demonstrated that lifestyle intervention can effectively improve early-stage thyroid disorders.
DOI: 10.1530/endoabs.37.EP962

EP963

Beware Carbimazole induced agranulocytosis in amiodarone induced thyrotoxicosis: recovery with Filgrastim

James O'Hare, Alwin Sebatian & Liam Casserly
Department of Medicine University Hospital Limerick, Limerick, Ireland.

Agranuloctosis is a rare and serious complication of Carbimazole. (risk $<1/10^6$ of population/year. It is associated with higher doses. We report two cases over 1 year in patients exposed to amiodarone.
Case 1: A 63 year old man with ischemic cardiomyopathy had been treated with amiodarone for atrial fibrillation for 3 years. 6 months after stopping he developed symptomatic thyrotoxicosis and started on carbimazole 60 mg per day. Thyroid T^c uptake was low. (Probable type 1 or mixed amiodarone thyrotoxicosis AIT). 3 months later he presented with sepsis and a neutrophil count of 0.010×10^9/l and was treated with Filgrastim and antibiotics. Granulocytes rose $>1.000\times10^9$/l on day nine of treatment Thyrotoxicosis resolved after 3 months on prednisolone and a short course of potassium perchlorate.
Case 2: A 72 year old female with atrial fibrillation, diabetes and ES renal disease previously on amiodarone for 2 years developed symptomatic thyrotoxicosis and treated with carbimazole 60 mg per day on a reducing regime. 2 months later she developed agranulocytosis and sepsis: neutrophil count: 0.010×10^9/l. Probable type 2 AIT induced thyrotoxicosis. She was treated with Filgrastim and antibiotics.Neutrophil count rose over 1.000×10^9 after 6 days. She became euthyroid after prednisone therapy.
Risk for carbimazole induced agranulocytosis may be do the combination of high doses and older age predisposing these patients to agranulocytosis. Because of the cross reactivity of antithyroid drugs treatment of thyrotoxicosis is particularly difficult with the risk of thyroid storm during sepsis. Amiodarone induced thyrotoxicosis can be slow to respond to antithyroid drugs and higher doses are often necessary. Both our patients had accelerated recovery with Filgrastim. We advise caution with high antithyroid drug doses in amiodarone induced thyrotoxicosis and suggest considering combined therapy early.
DOI: 10.1530/endoabs.37.EP963

EP964

Elevated TSH (in upper limit of normal) and insulin resistance

Mustafa Boz, Cuneyt Muderrisoglu, Esma Altunoglu, Feray Akbas, Fusun Erdenen & Hayri Polat
Istanbul Training and Reseach Hospital, Istanbul, Turkey.

Introduction
Level of TSH respond to fluctuations in serum free (FT_4) but remain in a very narrow individial range. Thyroid function tests are intrinsically linked to variables of insulin resistance and endothelial function. It is possible that underlying factors lead simultaneously to increased serum TSH, insulin resistance, even within current normal TSH levels.
Description of methods and design
We aimed intestigate the patients with upper limit TSH and insulin resistance in patients of our out-patients clinics of endocrinology where they were adressed for obesity. Serum insulin, C-peptide and TSH Levels were measured by chemiluminescence method on advia centour XP and HbA1C measured by immune – inhibition on Advia 2400 chemistry system (Siemens Healtcare Diagnostics Inc).
Results and conclusion
Some characteristics of study group (means $\pm$S.D.) (totaly 152 patients): age (years): 49.7$\pm$14.8, systolic blood pressure (mm/Hg): 128.8$\pm$19.2, diastolic blood pressure (mm/Hg): 78.3$\pm$9.6, fasting blood glucose (mg/dl): 110.3$\pm$48, HbA1C (%): 5.74$\pm$1.35, insulin (μU/ml): 12.2$\pm$11.4, C-peptide (ng/ml): 3.04$\pm$1.71, TSH (μIU/ml):2.56$\pm$2.7, FT_4 (ng/ml): 1.28$\pm$0.47, weight (kg): 84.5$\pm$18.7, BMI (kg/m^2): 32.2$\pm$7.5, circumference of waist (cm): 98.9$\pm$16.3, WHR (waist/hip ratio): 0.87$\pm$0.07. When we divided into two group according to TSH levels. We found hyperinsulinemia ($P<0.04$), elevated C-peptide levels ($P<0.01$), and WHR ($P<0.04$) in the second group. This findings could justify the increased risk for insulin resistance associated disorders, such as cardiovascular disease, observed in patients with high TSH levels.

DOI: 10.1530/endoabs.37.EP964

EP965

Hypothyroidism and platelet parameters evaluation: a preliminary study

Francesco Scavuzzo, Maria Ludovica Genna, Gianluca Nastri, Domenico Serino & Raffaele Volpe
Cardarelli Hospital, Naples, Italy.

According to the findings of recent epidemiological research, thyroid complaints are among the most frequent endocrine illnesses in Italy. Being positively correlated to MPV, the mean platelet volume, in subjects with hypothyroidism, it has been hypothesised in literature that TSH can have a probable prothrombotic effect. The mean platelet volume (MPV), PCT (plateletcrit), PDV (platelet distribution width) and P-LCR (platelet large scale ratio) indicate the dimensions of platelet circulating uniformity.
Aim
The study seeks to evaluate whether platelet indicators can undergo alterations in individuals affected by subclinical and clinical hypothyroidism.
Materials and methods
Between September and December 2014, 60 individuals of both sexes between 18 and 45, all unaffected by other pathologies, were enrolled: 20 with hypothyroidism, 20 with subclinical hypothyroidism and 20 controls. These consented to give peripheral venous blood samples for a complete emochromocitometric examination so as to determine platelet indicators, FT_3, FT_4, TSH thyroid hormones. The PT, APTT coagulative parameters and fibrinogen I levels of the single parameters were statistically evaluated with parametric analyses (l *t*-test of Student) and linear mixed model.
Results and considerations
Evaluation of the findings yielded that the P-LCT and PCT remained unaltered. Neither were in a state of conclamed hypothyroidism or sub-clinical hypothyroidism (*P*-value P-LCT$=$0.36 and 0.38, *P*-value PCT 0.75 and 0.40 respectively). However, the MPV and PDW seemed to undergo statistically significant modifications in patients with subclinical hypothyroidism (*P*-value 0.0000199–0.0159) and in patients with conclamed hypothyroidism (*P*-value 1.152 and 8.012), thus reflecting a hypothetical increase of thrombotic risk in such patients. With a view to being able to use the MPV and PDW as useful and affordable cardiovascular illness risk evaluation parameters, it is hoped that research upon more numerous sample populations may be forthcoming.

DOI: 10.1530/endoabs.37.EP965

EP966

Decreased ultrasound echogenity as a thyroid hypofunction marker

Dragan Dimic, Milena Velojic Golubovic, Milica Pesic & Sasa Radenkovic
Clinical Center Nis, Clinic of endocrinology, Nis, Serbia.

Objectives
The value of ultrasound in functional disorders can be significant. That is why the question arises on the use of ultrasound examination of thyroid gland and its echogenity as a screening method in early detection of disfunctions, primarily subclinical and clinical forms of hypothyreosis.
Methods
Testing included 328 patients. All examinees underwent ultrasound examination of thyroid gland, the blood was taken for determination of FT_4, TSH, TPOab andTGab. The patients were divided into two groups. Group A with normal echogenity of thyroid gland tissue, and B with decreased echogenity. Group B was divided into two subgroups, B1 with a mildly decreased and B2 with significantly decreased echogenity.
Results
TPO antibodies, TSH and TG antibodies positivity and their mean values in group B are significantly higher, as well as in subgroups B1 and B2, in relation to group A, $P<0.001$. In group A only two examinees (1%) were indicated with subclinical hypothyreosis. In group B the sublinical hypothyreosis was indicated in 21, while the clinical hypothyreosis was indicated in eight examinees. 29 (25%) suffered of thyroid gland altered function. In subgroup B1 eight examinees were indicated with subclinical and two with clinical hypothyreosis. Ten examinees (11%) suffered of altered thyroid function. In group B2 the subclinical was found in 13 examinees, while the clinical hypothyreosis was found in 6. 19 examinees (76%) suffered of altered thyroid function.
Conclusion
The ultrasound screening of thyroid gland plays important role in early detection of thyroid disfunction, i.e. sublinical and clinical hypothyreosis. Decreased ultrasound echogenity represents the significant marker of altered thyroid gland function. In these persons we have determined the high percentage of subclinical and clinical hypothyreosis frequency.

DOI: 10.1530/endoabs.37.EP966

EP967

Immunohistochemical expression of Claudin-1 in Hashimoto's thyroiditis and Graves' disease patients

Tatjana Zake[1], Sandra Skuja[1], Katrina Pekarska[1], Valerija Groma[1], Ilze Konrade[1] & Regina Kleina[2]
[1]Riga Stradins University, Riga, Latvia; [2]Riga Eastern Clinical University Hospital, Riga, Latvia.

Introduction
Autoimmune thyroid diseases, including Graves' disease (GD) and Hashimoto's thyroiditis (HT), are complex diseases combining genetic susceptibility and environmental encounters leading to the breakdown of immune tolerance. The relationship between thyroid cancer (TC) and HT has been proven (Guarino *et al.* 2010), and the antibody specific association has been demonstrated (Azizi *et al.* 2014). Overexpression of claudin-1 appears to be an early finding in TC.
Aim
To estimate expression of claudin-1 in the thyroid tissue of patients with HT and GD assessed by immunohistochemistry.
Materials and methods
Patients presenting 17 cases of HT, 7 of GD, and 11 cases of ordinary colloidal goiter with normal thyroid function were enrolled in this study. Immunohistochemical staining was performed using an anti-claudin-1 antibody. The expression levels were calculated semiquantitatively.
Results
Claudin-1 showed a circumferential membranous staining pattern in thyroid follicular epithelial cells. Positive claudin-1 expression (staining in $>5\%$ of the cells) was observed in 27 out of 35 cases (77.1%). The highest claudin-1 mean expression level was observed in HT patients, although six out of 17 cases showed negative claudin-1 expression. The mean claudin-1 expression level in HT and GD thyroid cells was calculated as 1.65$\pm$0.63 and 1.22$\pm$0.19 respectively, whereas, in control group it was estimated as 1.58$\pm$0.44. Only eight out of 35 cases (22.9%) showed claudin-1 positivity in $>50\%$ of the cells (score 4); six of which presented with HT and 2 – with colloidal goitre.
Conclusion
These results demonstrate that HT and GD patients display different junction protein expression patterns. The overexpression of claudin-1 in HT when compared to control tissues and GD patients may be interpreted similarly to overexpression of claudins in epithelial-derived cancers, including TC, however,

molecular mechanisms by which claudins affect tumourigenesis remain largely unknown.

DOI: 10.1530/endoabs.37.EP967

EP968

The effect of thyroid hormone replacement on treatment schedule

Mahmut Apaydin[1], Selvihan Beysel[1], Seyfullah Kan[1], Bekir Ucan[1], Esra Tutal[1], Taner Demirci[1], Mustafa Caliskan[1], Muhammed Kizilgul[1], Mustafa Ozbek[1], Erman Cakal[1] & Tuncay Delibasi[1,2]
[1]Department of Endocrinology and Metabolism, Diskapi Yildirim Beyazit Teaching and Research Hospital, Ankara, Turkey; [2]Department of Internal Medicine, School of Medicine (Kastamonu), Hacettepe University, Ankara, Turkey.

Introduction
Levothyroxine sodium (LT_4) is widely used thyroid hormone to treat hypothyroidism. It is generally recommended to take it in the morning and hungry. Several studies about timing of thyroid hormone administration have shown different effects on TSH and FT_4. The aim of this study is to determine the effects of timing of LT_4 administration on TSH and the clinical outcomes.
Method
The study group includes 65 patients with primary hypothyroidism who take a minimum dose of 50 mg levothyroxine sodium 30 min before the breakfast. Whether their serum TSH is within the laboratory reference range (0.5–5.75 mIU/l) has been examined. We have suggested the patients to take LT_4 at bed time instead in the morning and the patients have been observed for 3 months. Five patients have been excluded from the study for several reasons. At the end of the study parameters such as TSH, FT_4, lipid levels, BMI and clinical outcomes have been evaluated.
Results
Compared to the morning intake, LT_4 was taken at bedtime were an increase in free T_4 level of $0.06 + 0.20$ ($P = 0.025$) and an increase in body weight of $0.76 + 1.53$ ($P < 0.001$). The TSH levels have shown no significant difference between morning and bedtime intake of LT_4 ($P > 0.05$). When the clinical outcomes are evaluated, night sweating in ten patients (% 16.7; $P < 0.001$) and in eight patients (13.3%; $P < 0.001$)) increase in appetite have been observed.
Conclusions
Our study showed that use of LT_4 in the morning and at night had similar effects on serum TSH. However, bedtime intake of LT_4 has resulted in increase of sweating, appetite and weight.

DOI: 10.1530/endoabs.37.EP968

EP969

Estimation of iodine intake in pregnant women living in Northern Ireland using a validated food frequency questionnaire

Paul McMullan[1,2], Lesley Hamill[2], Jayne Woodside[2] & Karen Mullan[1]
[1]Belfast Health and Social Care Trust, Belfast, UK; [2]Queen's University, Belfast, UK.

Adequate iodine intake during pregnancy is required for the production of thyroid hormones and brain development in the foetus. Recent evidence has suggested re-emergence of mild iodine deficiency in the UK but there are few studies that have specifically looked at iodine intake in pregnant women. Current World Health Organisation recommendation is for 250 μg per day intake of iodine in pregnancy and the following are good sources of dietary iodine: 1 pint milk (~140–220 μg); one egg (~20 μg) and 100 g white fish (~115 μg). A cross-sectional survey was carried out to assess iodine intake amongst pregnant women (n = 145) living in Northern Ireland (NI). Iodine intake was estimated from a validated iodine specific food frequency questionnaire (FFQ). This 18 item semi-quantitative FFQ estimated iodine intake over the preceding two months and was repeated in 67 women during the second trimester and 36 in the third trimester. 70% of women consumed ≤½ pint (280 ml) milk per day although milk consumption increased with each trimester ($P < 0.01$). Egg consumption did not change significantly through pregnancy (18% none; 23% one egg/week). White fish intake was low with 77/145 (53%) eating fish never or ≤1 per month. Only 2/145 (1.4%) consumed white fish >1 per week. In the first trimester 76/143 (53%) women were taking an iodine containing supplement and this decreased through pregnancy ($P < 0.05$). The results suggest that pregnant women living in Northern Ireland have low intake of foods known to be rich sources of iodine. Only 53% of women took an iodine containing supplement during the early stages of pregnancy. The UK has no salt or food iodination programme and so public health messaging along with early ante-natal education is key to improving dietary intake of iodine at this important stage in foetal development.
Disclosure
Metabolic Unit Research Fund (Belfast Health and Social Care Trust).

DOI: 10.1530/endoabs.37.EP969

EP970

Iodine status of school girls living in Northern Ireland cities: a cross-sectional survey

Paul McMullan[1,2], Lesley Hamill[2], Jayne Woodside[2] & Karen Mullan[1]
[1]Belfast Health and Social Care Trust, Belfast, UK; [2]Queen's University, Belfast, UK.

Iodine deficiency is the most common cause of preventable mental impairment worldwide. Recent evidence suggests the re-emergence of mild iodine deficiency in the UK possibly due to changing farming practice. A recent multicentre survey in the UK reported that 68% of school girls were iodine deficient with the lowest levels seen in Northern Ireland (NI). Unlike many countries, the UK does not have a salt or food iodination programme. A cross-sectional survey of 264 schoolgirls, aged 14–15 years of age, was carried out in Belfast and Derry/Londonderry as the initial part of an Island of Ireland wide survey (seven centres). These are the two largest cities in NI and both located on the coast. Belfast is more southern with a latitude of 54.583 vs 54.998. Participants were surveyed in spring and winter months to look for seasonal differences. Urinary iodine levels were measured from morning spot urine samples using a standardised Sandell-Kolthoff colorimetry method. World Health Organisation defines deficiency as follows: mild 50–99 μg/l; moderate 20–49 μg/l; severe <20 μg/l. Median urinary iodine level was 119.1 μg/l (IQR 78.3–166.3). Ninety participants had mild deficiency (34%) while 14 had moderate deficiency (5.3%) and none surveyed had severe deficiency. There was no significant difference in urinary iodine level between spring and winter seasons and no difference between the two cities. Therefore of the schoolgirls surveyed in NI 39% were iodine deficient. These results are in keeping with the previous UK survey and completion of the study in the other five geographical areas will enable a clearer understanding of the extent of this public health issue.
Disclosure
Safefood (project reference 01-2013).

DOI: 10.1530/endoabs.37.EP970

EP971

The role of detecting BRAF T199A mutation in fine-needle aspiration biopsy in pre-operative diagnosis of nodular goitre

Anhelli Syrenicz[1], Monika Koziolek[1], Bartosz Kiedrowicz[1], Milosz Parczewski[2], Maria Stepaniuk[3,6], Elzbieta Andrysiak-Mamos[1], Joanna Obloza[4], Anna Sieradzka[1] & Agnieszka Binczak-Kuleta[5]
[1]Department of Endocrinology, Metabolic Diseases and Internal Diseases, Pomeranian Medical University, Szczecin, Poland; [2]Department of Infectious Diseases, Hepatology and Immune Deficiency, Pomeranian Medical University, Szczecin, Poland; [3]Department of Pathology, Pomeranian Medical University, Szczecin, Poland; [4]Department of Endocrinology, M.Curie Regional Hospital, Szczecin, Poland; [5]Department of Laboratory Diagnostics and Molecular Medicine, Pomeranian Medical University, Szczecin, Poland; [6]Westpomeranian Oncology Center, Szczecin, Poland.

Introduction
Molecular testing play increasingly a significant role in pre-operative diagnosis of nodular goiter, as standard methods may not give conclusive decision in choosing optimal treatment approach. BRAF gene mutations are often discovered in the cytological specimens among the patients with papillary thyroid cancer. The aim of the study was to assess the incidence of *BRAF* T1799A mutation in cellular specimens derived from fine needle aspiration biopsy (FNAB) of thyroid nodules.

Material/methods
85 women with nodular goiter were enrolled into the study. Using hormonal tests, autoantibodies and ultrasound, both hormonal thyroid dysfunction and autoimmune process were excluded. All the patients underwent FNAB of revealed nodules. We analyzed genomic DNA isolated from the thyroid lesions and peripheral blood. Standard methods of real-time amplification detection (real-time PCR) were used to analyze BRAF mutation, with the use of specific starters surrounding the mutated site.
Results
We found BRAF T1799A mutation in thyroid specimens of 6 (7.05%) subjects. In five of them, benign nature of the thyroid nodules was confirmed by FNAB of the lesions. This procedure was non-diagnostic in one subject and histopathology post-operative assessment confirmed papillary thyroid cancer.
Conclusion
The presence of BRAF mutation in FNAB cytological specimens of benign thyroid nodules may be useful to evaluate the risk of malignancy, support the diagnosis and choose treatment options of nodular goitre.
Disclosure
This work was supported by the Ministry of Science and Higher Education, Republic of Poland (grant number N N402466739).

DOI: 10.1530/endoabs.37.EP971

EP972

Pentraxin 3 levels in patients with Hashimoto disease

Unsal Aydin, Cavit Culha, Aynur Aktas, Muge Keskin, Muge Ozcan, Anara Karaca, Tulay Omma, Nese Ersoz Gulcelik, Gonul Koc & Yalcin Aral
Department of Endocrinology and Metabolism, Ankara Training and Research Hospital, Ankara, Turkey.

Pentraxin 3 (PTX3) is produced from several cell types in case of inflammation. PTX3 has been investigated in several autoimmune diseases. As Hashimoto disease is an autoimmune disease of thyroid, we investigated the role of PTX3 levels in patients with Hashimoto disease.
Objective
The aim of this study was to investigate the relationship between PTX3 and autoimmune thyroiditis.
Methods
The study subjects were classified as four groups. Group 1: Control group included 42 euthyroid healthy women with negative autoantibody. Group 2 included 27 euthyroid women with positive autoantibody. Group 3 included 46 subclinic hypothyroid women with positive autoantibody (TSH 5–10 mU/L). Group 4 included 39 hypothyroid women with positive autoantibody (TSH >10 mU/L). PTX3 values were measured with ELISA method.
Results
No significant difference was found for PTX3 level between patients with autoimmune thyroiditis and control group. The highest PTX3 level was determined in fourth group. There was a positive relation between PTX3 and TSH level in all groups. There was also a positive correlation between PTX3 and cortisol level.
Conclusion
This is the first study investigating the relationship between PTX3 and autoimmune thyroid disease. Although PTX3 levels were positively associated with TSH levels, we couldn't find any difference in PTX3 levels between our groups.
DOI: 10.1530/endoabs.37.EP972

EP973

Morphological and functional alterations of thyroid gland during treatment with tyrosine kinase inhibitors in advanced renal cell carcinoma

Laura Rizza[1], Elisa Giannetta[1], Emilia Sbardella[1], Rosa Lauretta[1], Daniele Gianfrilli[1], Andrea Lenzi[1], Flavia Longo[2] & Andrea M Isidori[1]
[1]Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy; [2]Department of Clinical Oncology, Sapienza University of Rome, Rome, Italy.

Background
Sunitinib (SUN) is a novel oral multitarget tyrosine-kinase inhibitor (TKI) that has demonstrated its efficacy in the treatment of metastatic renal cell carcinoma (mRCC). The thyroid dysfunction is one of the most common side effects of SUN. The mechanisms inducing thyroid dysfunction are still poorly understood.
Aim
Identify the incidence, severity, ultrasonographic changes and pattern of response of thyroid function tests during treatment with SUN.
Methods
This ongoing prospective observational study to date has completed the evaluation of 25 mRCC patients: ten women (59 ± 18 years) and 15 men (65.5 ± 7 years). 5/25 patients received LT_4 replacement therapy and 11/25 had thyroid nodules at enrollment. SUN was administered at daily dose of 50 mg (schedule 4/2). Thyroid function tests were assessed at baseline and at week-4 and -6 of each cycle, ultrasound at baseline and after the first and the third SUN cycle.
Results
we observed an increase in TSH values, most frequently after the second cycle of SUN (mean-TSH 17.05 ± 43.56 μUI/ml) and in older men (mean-TSH 91.95 ± 106.4 μUI/ml. TSH rose above normal range (0.35–4.94 μUI/ml) only in patients which were not on LT_4 replacement at enrollment. Half of untreated patients had an TSH elevation requiring LT_4 replacement after the first cycle; all of them required a further dosage increase after the second cycle. No dose-adjustment was needed in patients already on LT_4 at enrollment. In all patients, a volumetric reduction of thyroid lobes occurred at week-6. Ultrasound at week-18, detected the appearance of a hypoechoic solid nodule in one patient and a volumetric increase of pre-existing nodules in two other patients.
Conclusion
SUN is associated with thyroid functional and morphological changes occurring rapidly, within few weeks, in most but not all patients. Distinct individual patterns of response to TKI are identified allowing a better prognosis and management.
DOI: 10.1530/endoabs.37.EP973

EP974

Thyroid autoimmunity may effect on mean platelet volume

Isılay Kalan[1], Senay Arıkan Durmaz[1], Seyma Yavuz[2], Ayse Carlıoglu[3], Ramazan Cosar[2] & Aydın Cıfcı[2]
[1]Kırıkkale Unıversıtesı Tıp Fakultesı Ic Hastalıkları Anabılım Dalı, Endokrınolojı ve Metabolızma BD, Kırıkkale, Turkey; [2]Kırıkkale Unıversıtesı Tıp Fakultesı Ic Hastalıkları Anabılım Dalı, Kırıkkale, Turkey; [3]Kırıkkale Unıversıtesı Tıp Fakultesı Dermatolojı Anabılım Dalı, Kırıkkale, Turkey.

Aim
Mean platelet volume (MPV) is considered a new indicator of atherosclerosis. Activated platelets and subclinical inflammation predispose to create for atherosclerotic heart disease. Larger platelets are metabolically more active than smaller ones and have more protrombotic potential. We have recently demonstrated that MPV levels in Hashimoto's patients tend to be higher than healthy controls even if in euthyroid state. In present study we aimed to investigate a relationship between MPV and autoimmune thyroid disease.
Materials and method
patients with Hashimoto thyroiditis (HASH) (58 euthroid Hashimoto thyroiditis (EHASH) (mean age 43.4 ± 12.4 year)) and 42 hypothyroid (HPHASH) (mean age 46.7 ± 15.5 year)) and 81 patients with Graves disease (GD) (mean age 38.8 ± 13.5 year) who referred our endocrinology outpatient clinic due to high thyroid autoantibodies as antithyroid peroksidase (Anti-TPO) and/or antithyroglobuline (Anti-Tg) and/or TSH receptor antibody were included in the study. 57 (age-matched 46.4 ± 11.6 year) euthyroid control subjects were taken into the study. All study population were evaluated by hormonal and platelet parameters.
Results
Serum Anti-TPO levels in all study groups (EHASH, HPHASH, GD) were significantly higher than those control subjects ($P=0.01$, $P=0.0001$, $P=0.0001$ respectively). The MPV in patients with EHASH, HPHASH, GD were also found significantly higher than control group ($P=0.046$, $P=0.044$, $P=0.002$ respectively). No statistically significant differences were found between the other parameters such as the platelet count, platelet distribution width and plateletcrit. We found that MPV increased independently of presence of age, sex and TSH in chronic autoimmune thyroid diseases ($\beta=0.074$, $P=0.007$). There was a significant correlation between MPV and anti-TPO levels ($r=0.145$, $P=0.027$).

Discussion
Our findings suggest that change of autoimmunity in thyroid gland in patients with chronic autoimmune disease may be effect on MPV level as well as tend to create cardiovascular risk because of large platelets have more metabolically active.

DOI: 10.1530/endoabs.37.EP974

EP975

Body composition after treatment of subclinical hyperthyrodism

Diana Boj-Carceller[1], Alejandro Sanz-París[1], Johanna Espejo-Niño[2], Paloma de Castro-Hernández[1], Marta Monreal-Villanueva[1], Diego Alvarez-Ballano[1] & María Dolores Abós-Olivares[2]
[1]Department of Endocrinology and Nutrition, Hospital Universitario Miguel Servet, Zaragoza, Spain; [2]Department of Nuclear Medicine, Hospital Universitario Miguel Servet, Zaragoza, Spain.

Background
Subclinical hyperthyroidism (SHT) is associated with harmful effects on cardiovascular system, bone metabolism and progression to clinical hyperthyroidism. Loss of weight is a common fact in patients with clinical hyperthyroidism and of particular relevance in elderly patients, who are vulnerable to sarcopenia.
Objective
To assess changes in body composition after radioiodine therapy for SHT due to toxic nodular goitre.
Subjects and methods
Prospective controlled cohort study. Patients with persistent SHT due to toxic nodular goitre received a single fixed dose of ^{131}I (555 MBq). A control group was established with patients who preferred to delay treatment. Body composition (lean mass, fat mass and bone mineral content) was determined by dual-energy X-ray absorptiometry (DEXA) at baseline and 12 months after.
Results
Twenty-nine patients were studied (age 69.5±11.5; 75.9% women; BMI 27.1±5.7 kg/m^2; serum thyrotropin (TSH) 0.20±0.21 μUI/ml; serum free thyroxine (T_4) 1.01±0.19 ng/dl), 17 belonging to the treatment group and 12 to the control group. Study groups were comparable. No longitudinal changes in body composition were noted in either group, except for a trend to gain fat mass. However, when individuals with age >65 years were selected, only patients who received radioiodine therapy showed a significant increase in body weight (from 64.1±10.0 to 66.9±9.2 kg), BMI (from 27.3±4.8 to 28.7±4.5 kg/m^2), fat mass (from 26.1±8.5 to 27.8±7.9 kg), lean mass (from 36.3±0.4 to 37.4±0.4 kg) and skeletal muscle mass index (SMI) (from 6.0±0.6 to 6.3±0.6 kg/m^2).
Conclusions
Treatment of SHT seems to have positive effects on body composition in subjects older than 65 years. Weight gain reflects increases in both fat and lean mass.

DOI: 10.1530/endoabs.37.EP975

EP976

Efficacy of two different L-thyroxine formulations in dyspeptic patients with subclinical hypothyroidism

Danilo Ribichini[1], Berardino Vaira[2] & Renato Pasquali[1]
[1]Alma Mater University of Bologna, Endocrinology Unit S.Orsola-Malpighi Hospital, Bologna, Italy; [2]Alma Mater University of Bologna, Internal Medicine Unit S.Orsola-Malpighi Hospital, Bologna, Italy.

Levo-thyroxine (LT_4) formulations are available on tablets (TAB) or liquid solution (SOL). LT4 TAB absorption could be affected by several gastric diseases as Helicobacter pylori (HP) infection or chronic atrophic gastritis (CAG), instead no data are available on absorption of the LT_4 SOL in these conditions. The aim of the study was to compare the efficacy of TAB or SOL LT_4 formulations in patients with dyspeptic syndrome (DS) and subclinical hypothyroidism (SH) due to chronic autoimmune thyroiditis. 20 naïve patients (15 females, 5 males, 27 to 55 years), with DS and SH were included. All were firstly investigated by esophageal gastric duodenal endoscopy and urea-breath test and divided in: group A n=4 patients had HP infection; group B: n=4 with CAG; group C: n=6 with simple gastritis and n=6 with no organic alterations. LT_4 treatment was randomly (TAB or SOL) started at a fixed dose (1.5 μg/kg per day); TSH and FT_4 were assessed at T_0, T_3 and T_6 months of treatment. On group A HP eradication was performed at the 3rd month. In all groups, no difference in basal TSH levels were shown within patients assigned to different treatments (group A: TSH_{tab}=10.1±1.8, TSH_{sol}=9.6±2.2; group B: TSH_{tab}=7.1±1.2, TSH_{sol}=6.9±2.1; group C: TSH_{tab}=7.9±1.7, TSH_{sol}=8.1±2.1). At T_3, TSH values on group A (before eradication of HP) significantly decreased on patients treated with SOL, while on group B and C, equally decreased without difference within two formulations (group A: TSH_{tab}=7.8±2.6 vs TSH_{sol}=3.1±1.8, P<0.001; group B: TSH_{tab}=2.4±1, TSH_{sol}=2.6±1.2; group C: TSH_{tab}=1.7±1.4, TSH_{sol}=2.5±1.6). At T_6, TSH levels on group A (after eradication of HP) were in the normal range with no significant changes within two formulations; on group B and C, TSH levels were normal without significant difference within two formulations (group A: TSH_{tab}=2.5±2.6 vs TSH_{sol}=3.6±1.8, P=ns; group B: TSH_{tab}=3.5±2.2 vs TSH_{sol}=2.1±1.8, P=0.093; group C: TSH_{tab}=1.9±2.1, TSH_{sol}=2.0±1.7). In each groups, no differences were shown on FT_4 values within two formulations. In conclusion this preliminary report suggests that LT_4 TAB or SOL are equally efficient to treat SH in dyspeptic patients without gastric alterations or with simple gastritis or CAG, while LT_4 SOL seems to be more efficient than TAB in patients with HP infection, independent of its eradication.

DOI: 10.1530/endoabs.37.EP976

EP977

Clinical case of amyloid goitre due to idiopathic AA-amyloidosis

Dmitry Pasechnik[1,2], Elena Sinelnik[2], Natalya Volkova[1] & Maria Porksheyan[1]
[1]Rostov State Medical University, Rostov on Don, Russia; [2]Rostov Regional Hospital No. 2, Rostov on Don, Russia.

Introduction
Amyloid goitre is a rare cause of thyroid enlargement, especially as a reason of fast growth. Here we present unusual case of idiopathic AA-amyloidosis as a cause of rapidly growing goitre.
Clinical case: Patient 36-year-old presented with complaints of shortness of breath and deglutitive problems during 2 months. His medical history was notable for nephrotic syndrome due to AA-amyloid nephropathy and chronic hepatitis C that were diagnosed 8 years ago. At that time in order to determine the cause of AA amyloidosis, there were performed extensive laboratory evaluation, the results of which turned out barren of definitive diagnosis. The pathogenic and symptomatic treatment of nephrotic syndrome was prescribed. 3 years later he was diagnosed with terminal stage of chronic kidney disease, and chronic haemodialysis was started. Physical examination revealed considerably enlarged thyroid gland, and ultrasound was performed. The volume of gland was 163 ml, and there were detected three lesions about 2.5 cm in diameter. The results of thyroid ultrasound, which was performed because of screening for hyperparathyroidism 6 months ago, were normal. In order to determine the nature of lesions there was done fine-needle biopsy, the results of which were consistent with macro-microfollicular goiter. The thyroid function was normal (TSH 0.93 mU/l). Since there were objective signs of upper airway obstructive symptoms, there were performed thyroidectomy. Microscopically, the stroma contained deposits of amorphous material characteristic of amyloid. These deposits stained with Congo red and were apple green in colour when examined microscopically under polarised light. Immunohistochemical staining patterns were consistent with AA amyloid. There was extensive fat cell metaplasia in the thyroid interstitium.
Conclusion
The differential diagnosis of rapid thyroid enlargement should include amyloid goitre nevertheless the type of enlargement (in our case it was not typical diffuse manner) and amyloidosis duration if it is present.

DOI: 10.1530/endoabs.37.EP977

EP978

Pseudothrombocytopenia improved with antithyroid treatment in Graves' disease: a case report

Mehmet Muhittin Yalcin[1], Fusun Balos Toruner[1], Emre Arslan[1], Alev Altinova[1], Zubeyde Saygili[2], Sena Aksoy[2], Mujde Akturk[1], Zeynep Arzu Yegin[3] & Nuri Cakir[1]
[1]Gazi University Faculty of Medicine Department of Endocrinology and Metabolism, Ankara, Turkey; [2]Gazi University Faculty of Medicine Department of Internal Medicine, Ankara, Turkey; [3]Gazi University Faculty of Medicine Department of Hematology, Ankara, Turkey.

Thrombocytopenia can be seen rarely in Graves disease (GD). In this report we present a case of pseudothrombocytopenia in a 21-year-old woman who had hyperthyroidism due to GD. A 21-year-old female admitted to our clinic with symptoms such as hair loss, anxiety, nervousness and tremor in hands. Considering her symptoms, thyroid function tests were evaluated to screen for presence of hyperthyoidism. Her TSH level was low while free T_3 and free T_4 levels were elevated. There was no nodules seen in her thyroid ultrasonography. An increased radioiodine uptake was found in thyroid gland. Her thyroid receptor antibody (TRAB) was positive. In the light of all these results, GD was diagnosed. Before antithyroid treatment, a complete blood count and liver function tests were ordered. All the tests were normal except low platelet count. She had no bleeding history. Test was reordered using a citrate-containing tube and platelets were found low again. Aggrevated platelets were seen in peripheral smear showing that decreased platelet level was due to pseudothrombocytepenia. There was no history of herbal drugs,medicine or any other cause of pseudothrombocytopenia. Methimazole treatment was started. One month after therapy, thyroid function tests came back to normal levels, and TRAB turned to be negative. Interestingly platelet count were turned to be normal in blood tests using both EDTA-containing and citrate-containing tube. Repeated peripheral smear did not contain any aggregation of platelets. Pseudothrombocytopenia was described in only a few case reports in the active phase of some autoimmune diseases like systemic lupus eritamatosis. Our case is the first report of pseudothrombocytopenia in GD. We think that normalisation of platelet count after successful antithyroid treatment is important in the evaluation of these patients.

DOI: 10.1530/endoabs.37.EP978

EP979

Ogilvie's syndrome and myxoedema crisis: a case report

David Barbosa[2], Sara Freire[1], Nádia Simas[1], João Barreira[1], Emília Velhinho[1] & Glória Nunes da Silva[1]
[1]Serviço de Medicina 3, Centro Hospitalar de Lisboa Norte, Lisbon, Portugal; [2]Serviço de Endocrinologia, Diabetes e Metabolismo, Centro Hospitalar de Lisboa Norte, Lisbon, Portugal.

Introduction
Ogilvie's syndrome (acute colonic pseudo-obstruction) is a syndrome in which the clinical features resemble those of mechanical obstruction with massive colonic dilatation, in the absence of any demonstrable evidence of such an obstruction in the intestine. The exact pathophysiology of intestinal pseudo-obstruction remains to be elucidated. Current theories continue to suggest the idea of an imbalance in the autonomic nervous system. The initial therapy remains conservative with supportive measures (*Nil Per Os*, nasogastric decompression, correction of fluid, electrolyte and metabolic disorders, reduction or discontinuance of drugs that inhibit gastrointestinal motility, and treatment of infections), followed by neostigmine, decompressive colonoscopy and finally surgery if signs of ischemia, abdominal sepsis, or perforation are present.
Case presentation
A 51-year-old Caucasian female patient with a past medical history of hypothyroidism with poor adherence to therapy presented with symptoms of abdominal colic pain, distension and obstipation, associated with nausea, puffiness of the eyes, and adynamia. At observation the abdomen was distended, with normal bowel sounds, diffusely painful to palpation but without signs of peritoneal involvement. There was no altered mental status. Laboratory tests revealed increased creatinine and creatine kinase levels, normocytic normochromic anaemia, hypokalaemia, and normal glycaemic levels. Thyroid profile and ultrasonography were suggestive of primary hypothyroidism. Tomography images were consistent with Ogilvie's syndrome with proximal colonic dilatation until a cut off at the sigmoid, without any structural lesion visualised. The colonoscopy performed was normal. The patient underwent hormone replacement therapy, as well as supportive measures, evolving with progressive clinical and radiological improvement after a few days.
Conclusion
This case illustrates a rare association between myxoedema crisis and Ogilvie's syndrome and the importance of prompt recognition and treatment of reversible medical causes, after excluding mechanical large bowel obstruction.

DOI: 10.1530/endoabs.37.EP979

EP980

Effect of L-thyroxine on left ventricular function in subclinical hypothyroidism

Valentina Velkoska Nakova[1], Brankica Krstevska[2], Elizabeta Srbinovska Kostovska[3] & Gordana Pemovska[4]
[1]Clinical Hospital, Shtip, Macedonia; [2]University Clinic of Endocrinology, Diabetes and Metabolic Disorder, Skopje, Macedonia; [3]University Clinic of Cardiology, Skopje, Macedonia; [4]University Clinic of Cardiology, Skopje, Macedonia.

Introduction
Thyroid hormone deficiency can lead to the impairment of cardiac function. Whether subclinical hypothyroidism (ScH) is a risk factor for left ventricular (LV) dysfunction is controversial. Aim of the study was to assess whether ScH is associated with LV systolic and diastolic dysfunction and it's reversibility after treatment with L-thyroxine.
Material and methods
Twenty-seven consecutive patients with newly diagnosed ScH underwent laboratory analyses (TSH, fT_4, fT_3, anti-TPO, and anti-Tg antibodies), and a complete two-dimensional echocardiography study.
Results
Analysed patients has the following characteristics: age 41 ± 12 years, TSH 8.5 ± 2.7 mU/l before treatment, and TSH 2.07 ± 0.9 mU/l after an average follow-up period of 7.2 ± 1.9 months. Compared to baseline measurements, after 5 months euthyroid stage the duration of the A wave was shorter (112.18 ± 17.2 ms vs 112.18 ± 17.2 ms, $P < 0.01$), and the longitudinal global strain was higher ($-19.55 \pm 2.3\%$ vs $-20.07 \pm 2.7\%$, $P < 0.05$). Free T_4 positively correlated with E/A ratio ($r = 0.42$, $P < 0.05$) and fT_3 negatively correlated with DT ($r = -0.50$, $P < 0.05$). Univariant regression analysis showed a statistically significant independent effect of TSH on the E/e' lat, E/e' average, LVED vol, LA, and LA area.
Conclusion
Subclinical hypothyroidism is associated with systolic and diastolic LV dysfunction, as well as reducing global longitudinal LV systolic function. These alterations may be reversed by L-thyroxine.

DOI: 10.1530/endoabs.37.EP980

EP981

Is there any effect of the treatment on mean platelet volume in patients with hypothyroidism and hyperthyroidism?

Yildiz Okuturlar[1], Aliye Soylu[2], Enver Tekin[1], Meral Mert[3], Ozlem Harmankaya[1] & Abdulbaki Kumbasar[1]
[1]Department of Internal Medicine, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey; [2]Department of Gastroenterology, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey; [3]Department of Endocrinology and Metabolism, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey.

Introduction
Mean platelet volume (MPV) which is part of a complete blood count measures the platelet size. There are many studies in the literature that it is an indicator of platelet function in thrombotic and inflammatory diseases. However, the number of studies about changes in MPV after treatment in thyroid disease is very limited. In this study, we aimed to reveal the MPV change with treatment in patients with hypothyroidism and hyperthyroidism.
Materials and methods
After approval from the ethics committee 400 patients (mean age: 51.24 ± 13.62) were retrospectively examined. Two groups were created as 200 patients (21 males and 179 females) with hypothyroidism and 200 patients (26 males and 174 females) with hyperthyroidism. Regularly followed up patients having no other

inflammatory acute and chronic disease and without malignancy were included in the study. Before and after treatment in the outpatient follow MPV and TSH values were compared.
Results
TSH level is found 9.54 and 2.18 μIU/ml pre-treatment and post-treatment period respectively ($P<0.001$) in hypothyroid patients. Pre-treatment TSH level is 0.09 μIU/ml and also post-treatment level is 0.62 μIU/ml ($P<0.001$) in hyperthyroidism group. There is significant difference between MPV values before and after treatment in hypothyroidism and hyperthyroidism group and also MPV values increased in both groups after treatment ($P=0.001$).
Conclusion
It is known that MPV decreases in inflammatory events and MPV increases with regression of inflammation. Those results of hypothyroidism which is in group of autoimmune thyroid diseases can be interpreted in terms of the presence of inflammation. The reason for the changes in MPV in our study can be explained in terms of the effect of the treatment of inflammatory period.

DOI: 10.1530/endoabs.37.EP981

EP982

Co-occurrence of Graves' disease and immune thyrombocytopenia: a case report

Mehmet Muhittin Yalcin[1], Emre Arslan[1], Fusun Balos Toruner[1], Alev Altinova[1], Mujde Akturk[1], Burak Dumludag[2], Munci Yagci[3], Ilhan Yetkin[1] & Metin Arslan[1]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Gazi University, Ankara, Turkey; [2]Department of Internal Medicine, Faculty of Medicine, Gazi University, Ankara, Turkey; [3]Department of Hematology, Faculty of Medicine, Gazi University, Ankara, Turkey.

Also cytopenies can be established in the evaluation of Graves' disease (GD), isolated thrombocytopenia is very rare. Here, we present a case of immune thrombocytopenia incidentally found in the evaluation of GD. A 48-year-old female was admitted to our hospital with palpitation and anxiousness. The thyroid function tests were concordant with thyrotoxicosis. She had two subcentimetre nodules in the right thyroid lobe. Thyroid gland had increased iodine uptake. And thyroid scan showed a diffuse hyperactive thyroid gland. GD was diagnosed. She had isolated thyrombocytopenia in her complete blood count (37 000/μl). She had no history of bleeding, chronic illness, medication, or herbal drugs. Peripheral smear was concordant with platelet count. Her haemoglobin level was normal. Antinuclear antibody was negative. Immune thrombocytopenia was diagnosed. As she had platelet levels above 20 000/ml we decided to initially start methimazole therapy without steroid therapy. In the first month of methimazole therapy, platelet counts were defined between 25 000 and 45 000/μl. But 6 weeks after methimazole therapy, when her free T_4 and free T_3 levels were in the normal range, her platelet count began to decrease. Prednisolone treatment was initiated for immune thrombocytopenia. Platelet count rapidly increased to normal levels. Steroid therapy gradually tapered and stopped after two months. Four months after discontinuing steroid treatment, she is now euthyroid with methimazole therapy, and her platelet count is fluctuating between 100 000 and 120 000/μl.
Discussion
There were only a few case reports describing co-occurrence of GD and immune thrombocytopenia. A hypothesis of cross reaction between antithyroid antibodies and platelet epitopes were discussed. Although some literature supported this hypothesis, others did not. In our case report methimazole treatment was failed for improving platelet count despite successful normalisation of free thyroid hormone levels.

DOI: 10.1530/endoabs.37.EP982

EP983

Insulin resistance and low folate levels are associated with hyperthyroidism in Graves' disease

Celestino Neves[1], César Esteves[1], João Sérgio Neves[1], Oksana Sokhatska[2], Miguel Pereira[1], Carmo Palmares[2], Camila Dias[3], Davide Carvalho[1], Luís Delgado[2] & José Luís Medina[1]
[1]Endocrinology Service, Faculty of Medicine, São João Hospital, University of Porto, Porto, Portugal; [2]Immunology Department, Faculty of Medicine, São João Hospital, University of Porto, Porto, Portugal; [3]Department of Biostatistics and Medical Informatics, Faculty of Medicine, São João Hospital, University of Porto, Porto, Portugal.

Objective
To evaluate the interrelationships between thyroid function, insulin resistance, lipid profile, homocysteine, C-reactive protein (CRP), folic acid, and vitamin B12 levels, in Graves' disease (GD).
Methods
We recorded thyroid function tests, BMI, insulin resistance markers, lipid profile, homocysteine, CRP, folic acid, and vitamin B12 levels, in 104 subjects with GD in the first cycle of treatment with methimazole, 94% of whom were female. The subjects were classified into two groups: 49 patients were included in the hyperthyroid group (fT_3 >3.71 pg/ml and/or fT_4 >1.48 ng/dl, and TSH <0.35 UI/ml) and 55 in the euthyroid group. Statistical analysis was performed with Mann–Whitney *U* test, logistic regression, and Pearson's correlations test. Results are expressed as median and percentiles (25–75). A two-tailed *P* value <0.05 was considered significant.
Results
Significantly higher levels of TRAb (UI/ml) were found in the hyperthyroid patients (3.2 (1.5–12.1) vs 1.1 (0.5–2.0), $P<0.001$). The levels of folate (ng/ml) and WBISI were significantly lower in the hyperthyroid group (5.1 (3.6–6.5) vs 6.9 (5.1–9.4), $P=0.001$ and 4.39 (2.49–6.15) vs 5.50 (4.08–7.79), $P=0.015$). Across all patients, TSH levels were positively correlated with folate ($r=0.240$, $P=0.021$), HISI ($r=0.217$, $P=0.046$), and WBISI ($r=0.356$, $P=0.001$) and negatively correlated with TRAb ($r=-0.461$, $P<0.001$), HOMA-IR ($r=-0.218$, $P=0.045$), and IGI ($r=-0.313$, $P=0.004$). The levels of fT_3 and fT_4 were positively correlated with HOMA-IR ($r=0.284$, $P=0.008$ and $r=0.261$, $P=0.016$) and negatively correlated with HISI ($r=-0.283$, $P=0.009$ and $r=-0.261$, $P=0.016$) and WBISI ($r=-0.233$, $P=0.032$ and $r=-0.260$, $P=0.016$). Negative correlations were also found between fT_3 levels and QUICKI ($r=-0.281$, $P=0.009$) and between fT_4 levels and HDL-C ($r=-0.198$, $P=0.046$). In the hyperthyroid group we found significant correlations between fT_3 and Lp(a) ($r=0.367$, $P<0.05$). In the euthyroid group we found negative correlations between fT_3 and vitamin B12 ($r=-0.358$, $P<0.01$).
Conclusion
We found that patients with higher levels of TRAb and insulin resistance had a higher risk of being hyperthyroid in Graves' disease. On the other hand, patients with higher folate levels had a lower risk of being hyperthyroid.

DOI: 10.1530/endoabs.37.EP983

EP984

Urinary iodine concentrations in pregnant women with gestational and pregestational diabetes mellitus

Hana Vitkova[1], Katerina Anderlova[1,2], Veronika Radimerska[1], Jan Kratky[1], Tomas Fait[2] & Jan Jiskra[1]
[1]Third Department of Medicine, General University Hospital and First Faculty of Medicine, Charles University in Prague, Prague, Czech Republic; [2]Department of Obstetrics and Gynecology, General University Hospital and First Faculty of Medicine, Charles University in Prague, Prague, Czech Republic.

Introduction
Urinary iodine concentration (UIC) can reflex recent changes in iodine status and serve as a sensitive marker of current iodine intake. The cut-off value of UIC was determined as the level lower than 100 μg/l. Adequate median urinary iodine for iodine intake in pregnancy is 150–249 μg/l. The aim of this study was to map the situation of iodine intake in pregnant women with pregestational and gestational diabetes and to explore relationship with thyroid function.
Methods
We have measured UIC in 252 pregnant women screened positive for pregestational or gestational diabetes in second trimester of pregnancy. Currently, serum levels of autoantibodies against thyroid peroxidase (TPOAb) and thyroglobulin (TgAb), TSH, and free thyroxine (FT_4) were determined.
Results
Median UIC was 90.90 μg/l (range 20–4725 μg/l). In 222/252 (88.1%) women UIC was lower than 150 μg/l (median 85.70 μg/l) and in 151/252 (59.9%) was lower than 100 μg/l. UIC in the range appropriate with mild iodine deficiency (50–149 μg/l) was measured in 195/252 (76.2%) women and 27 (10.7%) values were found in the range of moderate deficiency (20–49 μg/l). Any value of UIC was lower than 20 μg/l. In nine women were measured levels in the adequate range for pregnant women (150–249 μg/l). In 21 women (8.3%) was UIC higher than 249 μg/l (median 305.1 μg/l). In women with the UIC <150 μg/l was found significantly higher serum TSH in comparison to them with UIC ≥150 μg/l (1.866 mIU/l vs 2.079 mIU/l, $P<0.001$).

Conclusion
In total 88.1% of women screened positive for gestational or pregestational diabetes were iodine deficient in second trimester of pregnancy and had slight elevation of serum TSH as compared to them with sufficient iodine intake.
Disclosure
This work was supported by the Research Programme Prvouk 25 of Charles University in Prague.
DOI: 10.1530/endoabs.37.EP984

EP985

Beware false positive lymph node biopsies in patients with chronic lymphocytic thyroiditis

Lorelei Salazar & Angelos Kyriacou
Salford Royal Foundation Trust, Greater Manchester, UK.

A 40-year-old lady who was 4 months *postpartum*, presented with clinical and biochemical features consistent with post partum thyroiditis associated with neck swelling. She had a family history of autoimmune thyroid disease. She underwent ultrasound guided fine-needle aspiration (FNA) biopsy which was reported as Thy3f and listed for diagnostic hemithyroidectomy. She presented to us for a second opinion. She was on replacement therapy and the anterior neck swelling has resolved. Thyroid antibodies were negative. Thyroid ultrasound was repeated showing a diffusely lobular thyroid consistent with background thyroiditis with associated lymphadenopathy. The isthmus 'thyroid nodule' that was previously biopsied was noted to be extrathyroidal isthmus lymph nodes in close proximity to the thyroid. Patient was discussed in a multidisciplinary meeting (MDT) with confirmation that the original cytology was reflective of lymphocytic thyroiditis. She was advised that surgery was not indicated but she will be actively monitored clinically.
Sonographic features of chronic lymphocytic thyroiditis (CLT) include the following: hypoechoic and heterogeneous, pseudomicronodular ('swiss cheese' or 'honeycomb' pattern), pseudomacronodular, profoundly hypoechoic, developing fibrosis, hyperechoic, and speckled. Pseudomicronodular appearances may be confused with a multi-nodular goitre. With the pseudomacronodular pattern the area of inflammation is larger. The skilled sonographer need to be able to appreciate both these patterns as they may be misinterpreted for thyroid nodules. Reactive lymph nodes are almost universally found in CLT; they are commonly found in the pretracheal and paratracheal region as well as at levels III and IV. Given the higher prevalence of papillary thyroid cancer in CLT, such lymph nodes need to be distinguished from malignant lymph nodes using the same sonographic criteria as per patients without CLT. Isthmus lymph nodes can be mistaken for thyroid nodules given their close proximity to the thyroid potentially leading to unnecessary investigations and treatment.

DOI: 10.1530/endoabs.37.EP985

EP986

Propylthiouracil induced anti-neutrophil cytoplasmic antibody-associated vasculitis with skin lesions and granulocytopenia

Seher Tanrikulu, Burak Ince, Özlem Soyluk Selcukbiricik, Sakin Tekin, Ferihan Aral & Refik Tanakol
Division of Endocrinology and Metabolism, Department of Internal Medicine, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey.

Propylthiouracil (PTU) is a widely used drug, and can cause drug-induced vasculitis which is characterized by inflammation and cellular infiltration of small vessels and presence of anti-neutrophil cytoplasmic antibodies (ANCA). We report a case of perinuclear antineutrophil cytoplasmic antibody-associated vasculitis developed during treatment with PTU for Graves' disease. A 58-year-old woman admitted to the Emergency Department with painful necrotic lesion at her right ear and left arm for 15 days. Ear lesions were considered as ecthyma gangrenosum in an ENT clinic 10 days ago and anti-pseudomonal treatment had begun but no ameloriation observed. Her medical history was significant for type 2 diabetes for 12 years and Graves' disease for 4 years. There had been a similar lesion at her left ear 6 months ago resulted with auto-amputation. She had been using PTU 100 mg/day and pre-mixed insulin injection twice a day. We found non-tender, mobile cervical lymphadenopathies, enlarged liver and spleen together with ear lesions in physical examination. Her laboratory tests revealed normal thyroid function, leukopenia, neutropenia and normochrom normocytic anaemia, high CRP and sedimentation with p-ANCA and anti-MPO positivity. Biopsy of the affected skin revealed leukocytoclastic vasculitis. As additional tests excluded systemic vasculitis, propylthiouracil-induced vasculitis was diagnosed. Propylthiouracil was discontinued and the skin lesions disappeared, granulocytopenia has revealed over time without the need of any specific therapy.
Conclusion
Physicians and also the patients should be aware of the major adverse reactions of anti-thyroid drugs.

DOI: 10.1530/endoabs.37.EP986

EP987

Haemorrhagic thyroid cyst after breathing exercise

Abbi Lulsegged[1], Mufaddal Moonim[2] & Rose Ngu[2]
[1]Kings College Hospital NHS Foundation Trust, Farnborough, Kent, UK; [2]Guys and St Thomas NHS Foundation Trust, London, UK.

A 40-year-old gentleman was referred with sudden onset discomfort in the neck associated with the development of a lump. Earlier that morning he had carried out breathing exercise known as surya krishna at 0600 h and noticed the lump 3 h later whilst shaving. Thyroid USS showed a right-sided thyroid cyst, aspiration of which yielded haemorrhagic contents. FNA of the solid component of the wall did not reveal any malignant cells. The fluid re-accumulated with pressure symptoms including a gritty discomfort when talking, pain and heaviness in this region. Repeat scan did not reveal any significant changes in the appearance of the thyroid cyst. Surya krishna is a breathing exercise lasting 30–60 min with times of hyperventilation and other times of slow breathing. He recalled experiencing pins and needles, numbness and tingling with the hyperventilation but felt energetic at the end of the session. However, at the beginning of the session there is an emphasis placed on breathing through the throat and he remembered exerting a certain pressure in the throat region when doing this. We hypothesise that the pressures involved during the breathing exercises may have been sufficient to cause haemorrhaging within a thyroid nodule. The authors have seen two other cases presenting in a similar manner.

DOI: 10.1530/endoabs.37.EP987

EP988

Levothyroxine therapy in comparison: fixed vs alternating dosage in subclinical hypothyroidism

Renato Pastore[1], Amalia Cannuccia[2] & Frontoni Simona[1,2]
[1]Ospedale S. Giovanni Calibita, Fatebenefratelli, Isola Tiberina, Roma, Italy; [2]Department of Systems Medicine, Tor Vergata University, Roma, Italy.

Introduction
Oral levothyroxine (L-T_4) is the standard treatment for hypothyroidism and serum TSH represents the best marker for assessing the proper L-T_4 dose. The absorption and bioequivalence of different commercial L-T_4 preparations might be variable. The aim of this study is to compare the efficacy of L-T_4 using alternating doses vs fixed ones.
Methods
Fifty-eight patients with primary hypothyroidism receiving L-T_4 therapy. The inclusion criteria were as follows: i) age range between 23 and 75 years and ii) patients with subclinical hypothyroidism (TSH level between 2.5 and4.5 mU), treated with L-T_4 oral solution at alternating dosages on consecutively days (75 μg/100 μg, group O) or soft capsules (88 μg/day daily, group T), for at least 6 months. The exclusion criteria were as follows: i) pregnancy or lactation; ii) patients with chronic diseases, such as cardiac (coronary disease or arrhythmias), pulmonary, gastrointestinal (malabsorption disorders), and renal disorders or malignancy; and iii) medications that could interfere with L-T_4 absorption.
Results
According to ANOVA for repeated measure with treatment (T vs O group) as between-subjects factor and time (baseline, 45, 90, and 180 days) as within-subjects factor, a significant interaction treatment×time was found ($F=3.673$, Greenhouse-Geisser df = 1.9, 184.6, $P=0.028$), indicating two different trends of

TSH in T and O groups. Contrast analysis (each time vs baseline) showed a stronger TSH decrease after soft capsules at 180 days (O group 2.17±0.55 and T group 1.67±0.59).
Discussion
Our preliminary observation seems to show a possible greater efficacy of L-T_4 at fixed dosage vs alternating and consecutive dosage, as suggested by significant greater decrease of TSH levels in group T. This finding could be related to an improving of adherence to L-T_4 therapy at fixed dosage. Treatment at alternating dosage on consecutive days may not always be accurate. However, prolongation of follow-up is needed to confirm our data.

DOI: 10.1530/endoabs.37.EP988

EP989

The relationship between vitamin D deficiency and thyroid autoimmunity in Graves' disease

Tuğba Arkan
Kocaeli Derince Education and Research Hospital, Kocaeli, Turkey.

Context
Graves' disease (GD) is the most common cause of hyperthyroidism. It occurs more commonly amongst women, smokers and patients with other autoimmune diseases or a family history of thyroid autoimmunity. Peak incidence occurs between 40 and 60 years of age but any age group may be affected. Vitamin D deficiency has been reported to link with a variety of autoimmune diseases. However, the relationship between the thyroid autoimmunity in GD and vitamin D deficiency is unclear.
Objective
We aimed to investigate the association of vitamin D and TSH receptor antibody levels (TRab) with GD.
Design and setting
This was a cross-sectional study conducted in education and research hospital. A total of 67 patients with GD (30 men and 37 women) along with 53 age-matched non-GD controls participated in the study.
Main outcome measures
TSH, free triodothyronine (FT_3), free thyroxine (FT_4), thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAb), thyrotrophin receptor antibody (TRAb), parathyroid hormone (PTH), calcium, and 25-hydroxyvitamin D (25(OH)D) levels were measured.
Results
25(OH)D levels were significantly lower in the GD group, compared with non-GD control group ($P<0.001$). 25(OH)D levels was inversely correlated with TRab levels ($r=-0.38$, $P<0.001$). However, our results did not show a correlation between the levels of 25(OH)D and the levels TPOAb, TGAb, FT_3, FT_4, and TSH. The levels of PTH in serum were increased in TRAb positive GD patients compared to control subjects ($P<0.001$). Logistic regression analysis results indicated that 25(OH)D levels were not a significant risk factor for developing GD.
Conclusion
In patients with GD, low vitamin D status might be cause of increased titres of TRAb, suggesting a possible link between vitamin D status and increased thyroid autoimmunity in GD.

DOI: 10.1530/endoabs.37.EP989

EP990

Thyroid hormone resistance: a case report

Pinar Sisman[1], Hande Peynirci[1], Ozen Oz Gul[1], Soner Cander[2], Esra Nur Bulbul[3], Erdinc Erturk[1] & Canan Ersoy[1]
[1]Department of Endocrinology and Metabolism, Uludag University Medical School, Bursa, Turkey; [2]Clinic of Endocrinology and Metabolism, Sevket Yilmaz Training and Research Hospital, Bursa, Turkey; [3]Department of Internal Medicine, Uludag University Medical School, Bursa, Turkey.

Classic thyroid hormone resistance (THR) occurs per every 400 000 live birth. THR should be considered along with TSH-producing adenomas when normal or high levels of TSH not consistent with hyperthyroidism is present. A 45-year-old female patient who was operated three times for multinodulary goitre had been treated with L-thyroxine. Mamillary biopsy had performed after detection of mass localized in right breast by mammography performed during regular follow-up, then right radical mastectomy was performed due to the diagnosis of ductal carcinoma. In thyroid USG examination, it was found that there were three to four nodules in right thyroid lobe sized 9×6.5 mm and nodules with hypoechoic solid-nature which largest of them was 16×11 mm in left thyroid lobe. In addition, there were also ovoid-shaped lymph nodes with fatty hiluses in both cervical lymphoid chains as two of them (largest one sized 26×5 mm) in right zone 3 and three of them (largest one sized 25×6 mm) in left zone 3. Thin needle aspiration biopsy was performed on thyroid nodules and cervical lymph nodes. Results were benign. Cella magnetic resonance imaging (MRI) was performed with diagnosis of secondary hyperthyroidism after detection of elevated TSH, fT_3, and fT_4 levels in thyroid tests. In cella MRI, it was found that there was an adenoma sized 11×9×10 mm in hypophysis gland. Other anterior hypophysis hormones were normal. There were no eyesight pathology. L-thyroxine treatment was ceased due to the euthyroid status of the patient. During tests performed for excluding THR, it was found that alfa subunit (ASU) level was in normal range (0.35) and molar ASU/TSH ratio was below 1. These results were consistent with THR. Then, TRH stimulation test was planned. TSH levels at 0, 15, 30, 45, and 60 min after TRH administration were obtained. It was observed that there was an extensive response consistent with THR in TSH levels with TRH test (TSH at 0 min: 8 mIU/ml, TSH at 15 min: 57 mIU/ml, TSH at 30 min: 76 mIU/ml, TSH at 45 min: 75 mIU/ml, and TSH at 60 min: 67 mIU/ml). Hypothyroidism symptoms were not observed in follow-up without medication. Adenoma size had not been changed in control sella MRI. Anterior hypophysis hormones were in normal range. Patient was enrolled in follow-up with the diagnosis of THR and non-functional hypophysis adenoma. In clinical practice, differentiation between TSH-secreting adenomas and THR is quite difficult. Predominance of hyperthyroidism symptoms and presence of macroadenoma in hypophysis make the possibility of TSH-secreting adenoma more convincing. However, most of the patients are asymptomatic. Considerable elevations in TSH levels increase the possibility of TSH-secreting adenoma although thyroid function tests are mostly same in both of these pathologies. TRH stimulation test is the most valuable test for diagnosing. Its sensitivity and specificity were reported as 90% and 80–90% respectively. In conclusion, THR should be considered before diagnosing as TSH-secreting adenoma in patients evaluated for secondary hyperthyroidism and identified with hypophysis adenoma.

DOI: 10.1530/endoabs.37.EP990

EP991

Relationship of thyroid function and central obesity

Lina Zabuliene[1,2], Agne Petrenaite[3], Ieva Minkeviciute[3] & Jurgita Urboniene[4]
[1]Clinics of Rheumatology, Traumatology – Orthopaedics and Reconstructive Surgery, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [2]Antakalnio Outpatient Clinic, Vilnius, Lithuania; [3]Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [4]Infectious Diseases and Tuberculosis Hospital, Vilnius University Hospital Santariskiu Klinikos, Vilnius, Lithuania.

The objective of the study was to investigate association between BMI, waist circumference, and measures of thyroid function among euthyroid adult women.
Material and methods
We analysed retrospective data of 119 euthyroid women participating in Lithuanian screening and prevention program for patients with high cardiovascular risk at Vilnius Antakalnio Outpatient Clinic from Jul 2013 to Dec 2013. Glucose, lipid profile, TSH, and fT_4 tests and ultrasound of thyroid gland records were investigated and thyroid gland volume was calculated using formula: thyroid volume = height × width × depth × correction factor (as 0.524).
Results
Mean patients age was 57.04±4.56, BMI 28.86±5.53 kg/m^2, waist circumference 88.40±12.24 cm, TSH 1.81±0.92 mIU/l, fT_4 12.84±2.89 pmol/l, and mean thyroid gland volume 14 464.46±6453.74 mm^3. 36.1% of women were obese and 41.2% overweight. Mean TSH and thyroid volume did not differ between groups of obese, overweight and normal weight women. TSH inversely correlated with thyroid gland volume ($r=-245$, $P=0.044$), fT4 ($r=-0.471$, $P=0.042$), and positively correlated with waist circumference ($r=0.210$, $P=0.036$) and BMI ($r=0.184$, $P=0.045$). After adjusting for age, presents of diabetes and dyslipidaemia significant positive association was observed between TSH and waist circumference ($B=0.17$, $P=0.029$).

Conclusions
We found that measures of overall and central adiposity were associated with higher circulating levels of TSH in euthyroid women. Although, weight loss and weight gain are well-known consequences of overt thyroid dysfunction, our results suggest that, within the euthyroid range, excess body weight and especially central obesity may induce changes in thyroid hormone levels.

DOI: 10.1530/endoabs.37.EP991

EP992

Ultrasonographic and cytopathological characteristics of thyroid nodules in Graves' disease

Cuneyd Anil, Nazli Gulsoy Kirnap, Ozlem Turhan Iyidir, Sevde Nur Firat & Neslihan Bascil Tutuncu
Faculty of Medicine, Baskent University, Ankara, Turkey.

Introduction
The risk of malignancy has often been reported to be more frequent in Graves' disease (GD) than non-autoimmune thyroid nodules. However, frequency of thyroid nodules, diagnostic yield of fine-needle aspiration (FNA), and their potential for bearing malignancy in GD are still debatable issues. We aimed to determine the prevalence, ultrasonographic and cytological features, and the rate of malignancy outcome of thyroid nodules in a group of patients with GD.
Methods
This was a single center retrospective study. All patients with GD followed up in the Outpatient Clinic of Department of Endocrinology between 2008 and 2013 were included. Thyroid hormone, thyroid autoantibody, TSH receptor antibody (TRAb) levels of all cases during diagnosis were recorded. Basic ultrasonographic data, cytological results of every nodule which underwent fna, and the histopathological data were also recorded.
Results
175 cases (132 females) with mean $\pm$ S.D. age 45.9 $\pm$ 15.8 were included. 58.8% of the whole group were TRAb positive. 81.1% ($n=142$) of the patients were treated with anti-thyroid drugs. 14.3% ($n=25$) were finally treated with radioactive iodine with a median (min–max) dose of 12 mCi (5–20). 40% ($n=70$) of the cases had totally 134 thyroid nodules. The median (min–max) value of maximum diameter of thyroid nodules was 10.0 (3–54) mm. 14.8% of the nodules owned microcalcifications. 23% ($n=28$) nodules underwent FNA. Cytopathology revealed that 24 were benign, two were indeterminate, and the last two were non-diagnostic, both of which were also eventually benign in repeat aspirations. The indeterminate nodules went to surgery, which turned out to be benign. Eight additional patients underwent surgery for ablative purposes; only one turned out to be malignant, which was incidental.
Conclusion
Nodular goitre is prevalent in GD. Diagnostic yield of fna may not be so low; malignancy rates do not seem to be high in this group of patients.

DOI: 10.1530/endoabs.37.EP992

EP993

Thyroid disorders in patients with type 2 diabetes mellitus

Ayhan Zengi[1], Serap Unal Tilki[3] & Timur Kose[2]
[1]Endocrinology and Metabolism, Isparta State Hospital, Isparta, Turkey; [2]Biostatistic, Ege University, Izmir, Turkey; [3]Internal Medicine, Isparta State Hospital, Isparta, Turkey.

Aim
Increased thyroid volume and thyroid dysfunction (TD) in diabetics have been reported. The aim of this study is to investigate the prevalence of thyroid disorders in patients with type 2 diabetes mellitus in formerly iodine deficient area.
Methods
We included 131 (73 females and 58 males) diabetics without a history of previous thyroid disease and symptoms. The demographic, medical and clinical data, laboratory results (fasting plasma glucose (FPG), HbA1c, lipid profile, TSH, free thyroxine (fT_4), and free triiodothyronine (FT_3)) were recorded. The result of thyroid function was classified as subclinical hyperthyroidism (Sc-hyper) (TSH $\leq$0.5 mIU/l, FT_4 and FT_3: normal), euthyroidism (TSH: 0.5–4, FT_4 and FT_3: normal), and subclinical hypothyroidism (Sc-hypo) (TSH: 4.1–9.9, FT_4 and FT_3: normal). All participants were evaluated by thyroid ultrasonography (US) and thyroid volume (TV) were calculated by standard formula.
Results
There is a significant difference between females and males with respect to age, smoking habit, and BMI. No significant differences were found between two groups with respect to diabetes duration, FPG, HbA1c, lipids levels, and thyroid function. Sc-hyper, euthyroidism, and sc-hypo were detected in 15 (11.4%), 107 (81.7%), and 9 (6.9%) patients respectively. US findings except TV were similar in two groups. Although, TV was higher in males than females, the diameter of dominant nodule was not different. In all patients, the frequencies of normal US, multinodular goitre (MNG), nodular goitre (NG), diffuse goitre (DG), and thyroiditis with or without nodule were 24 (18.3%), 51 (38.9%), 27 (20.6%), 10 (7.6%), and 19 (14.6%) respectively.
Conclusion
The most common thyroid disorder in diabetics is hypothyroidism. Although, the prevalence of thyroid dysfunction in our patients is concordant with previous results, sc-hyper is more prevalent than sc-hypo. According to our results, 81.7% of diabetics had thyroid gland abnormality by US. In light of these results, all diabetics should be evaluated for thyroid disorders.

DOI: 10.1530/endoabs.37.EP993

EP994

The occurrence of newly diagnosed thyroid diseases during 13 years follow-up

Monika Buziak-Bereza[1,2], Malgorzata Trofimiuk-Muldner[1,2], Maciej Kolodziej[2] & Alicja Hubalewska-Dydejczyk[1,2]
[1]Chair and Department of Endocrinology, Jagiellonian Univesity Medical College, Krakow, Poland; [2]Endocrinology Department, University Hospital in Krakow, Krakow, Poland.

The increase in thyroid disease frequency has been observed recently. It may be attributed to the changing iodine status, endocrine disruptors, as well as better availability of ultrasound and laboratory tests. The aim of the study was to assess the occurrence of newly recognized thyroid diseases during long-term follow-up.
Material and methods
Study was carried out in 2010–2012 in Krakow area. It included 266 patients aged 23–81 years (168 females and 98 males) out of 548 subjects with no thyroid diseases detected during previous survey (1997–1999). In each patient thyroid ultrasound was performed, and TSH, FT_4, and ATPO levels were assessed.
Results
During 13 years primary hypothyroidism requiring treatment with levothyroxine was detected in 29 subjects (10.9%). In additional 13 cases subclinical hypothyroidism was recognised (4.9%). Elevated titer of ATPO antibodies was detected in 40 subjects (15%). Two subjects had already been treated with radioactive iodine due to hyperthyroidism. The new case of hyperthyroidism was diagnosed in one person during the survey. In two subjects thyroidectomy had been performed during 13 years preceding the study (including one case of differentiated thyroid cancer). In 112 (42.8%) of studied persons (45.5% of females and 38.1% of males) nodular goiter was recognized: solitary nodule in 19.1% and multinodular goiter in 23.7%. In one male papillary thyroid cancer was detected.
Conclusions
During about 10-year follow-up new thyroid pathology may be detected in up to 50% of studied population.
Disclosure
This work was supperted by Jagiellonian University Medical College grant.

DOI: 10.1530/endoabs.37.EP994

EP995

E-selectin in women with autoimmune thyroiditis and the relationships with metabolic syndrome

Lucyna Sieminska[1], Beata Kos-Kudla[1], Bogdan Marek[1], Mariusz Nowak[1], Dariusz Kajdaniuk[1], Wanda Foltyn[1], Krzysztof Walczak[2] & Artur Borowski[3]
[1]Department of Pathophysiology and Endocrinology, Medical University of Silesia, Katowice, Poland; [2]Regional Railway Hospital, Katowice, Poland; [3]The Silesia Urology Centre Urovita, Chorzow, Poland.

Autoimmune thyroiditis (AIT) is characterised by infiltration of the thyroid by lymphocytes and other immune cells. Autoantibodies to thyroid-specific antigens:

thyroglobulin (TG) and thyroperoxidase (TPO) are also produced. The penetration of inflammatory cells into target organ is regulated by cytokines and adhesion molecules expressed on thyroid endothelial cells. E-selectin is one of the selectin family, and is responsible for interaction between leukocytes and endothelium and facilitates the accumulation of inflammation cells in thyroid gland. It is suggested that chronic inflammation and endothelial dysfunction can lead to increased cardiovascular risk and metabolic syndrome (MS) in AIT.
Aim
To investigate whether AIT is associated with elevated serum levels of E-selectin; to examine relationships between E-selectin, thyroid function, and different risk factors – components of MS.
Materials and methods
Two hundred and fifty-eight postmenopausal, euthyroid women were enrolled into the study. In 76 women AIT was recognised as the presence of elevated at least one of thyroid antibodies (TPO-Abs and TG-Abs) and the presence of typical thyroid sonography. One hundred and eighty-two women without AIT were control group. Anthropometric measurements were conducted (BMI and WHR) and blood pressure was measured. In all subjects were assessed: lipid profile, glucose, TSH, fT_4, TPO-Ab, TG-Ab, and E-selectin concentrations. Thyroid ultrasound scan was performed. The diagnosis of MS was performed using AHA/NHLBI criteria.
Results
When we compared AIT women and control group there were no differences in serum E-selectin concentrations. E-selectin was higher in MS for the two groups, but the prevalence of MS was similar. When we analysed all studied women, E-selectin positively correlated with BMI, WHR, and negatively with cHDL and fT_4. AIT was associated with elevated TSH.
Conclusions
In our study E-selectin was increased in metabolic syndrome, in relationships with obesity, visceral adiposity and lower fT_4, but was not related to thyroid autoimmunity.

DOI: 10.1530/endoabs.37.EP995

EP996

Ultrasound-guided fine-needle aspiration biopsy is an efficient diagnostic tool in thyroid nodules

Ioana Armasu[1], Delia Ciobanu[2], Andra Istrate[3], Ioana Vasiliu[4], Lidia Ionescu[5], Cristina Preda[1], Voichita Mogos[1] & Carmen Vulpoi[1]
[1]Department of Endocrinology, University of Medicine and Pharmacy 'Gr.T. Popa', Iasi, Romania; [2]Department of Morphopathology, University of Medicine and Pharmacy 'Gr.T. Popa', Iasi, Romania; [3]Department of Internal Medicine, University of Medicine and Pharmacy 'Gr.T. Popa', Iasi, Romania; [4]Department of Physiology, University of Medicine and Pharmacy 'Gr.T. Popa', Iasi, Romania; [5]Department of General Surgery, University of Medicine and Pharmacy 'Gr.T. Popa', Iasi, Romania.

Introduction
Thyroid nodules are commonly encountered in clinical practice, the main diagnostic problem being the benign or malignant nature of the nodules. Fine-needle aspiration biopsy (FNAB) is a standard diagnostic test for evaluating thyroid nodules. Several studies have showed that the use of ultrasound guidance (US-FNAB) improves the diagnostic accuracy of aspiration biopsies in comparison with palpation guidance (P-FNAB) alone.
Patients and methods
We performed a retrospective study to compare the efficacy of US-FNAB of thyroid nodules with that of P-FNAB. Study group included patients referred to Endocrinology Department for assessment of thyroid nodular disease who underent FNAB by palpation from 2000 to 2001 and under echoguidance in 2009–2012. In order to avoid differences due to nodules size we have selected only palpable nodules in both groups. Thyroid examinations, ultrasound imaging, and aspiration biopsies were performed by the same endocrinologist. Histopathologic and cytologic diagnoses were compared for patients who were operated.
Results
Study sample consisted of 403 patients. P-FNAB was performed in 106 patients (of which 32 underwent thyroidectomy), and US-FNAB in 297 patients (58 operated). Excepting for moderate local pain in some cases, no adverse effects were noticed. Cytologic diagnostic accuracy rate was 83.87 and 90.19% for P-FNAB and US-FNAB respectively. With use of ultrasound guidance, sensitivity (85.71% for US-FNAB and 50% for P-FNAB), positive predictive value (60% vs 40%), and negative predictive value (97.56% vs 92.3%) were increased significantly and the false-negative rate was significantly reduced (14.28% vs 50%).
Conclusions
FNAB is an essential diagnostic tool in the management of thyroid nodules. US-FNAB improved the cytologic diagnostic accuracy, sensitivity, and positive predictive value and reduced the false-negative rate in comparison with P-FNAB. Therefore, practice guidelines should universally recommend US-FNAB in the management of thyroid nodules, permitting an accurate preoperatory diagnostic and avoiding numerous unnecessary surgical interventions.

DOI: 10.1530/endoabs.37.EP996

EP997

Two cases with primary thyroid lymphoma developed on the basis of Hashimoto's thyroiditis

Hande Peynirci[1], Pinar Sisman[1], Cigdem Aksu[2], Ozen Oz Gul[1], Soner Cander[3], Erdinc Erturk[1] & Canan Ersoy[1]
[1]Department of Endocrinology and Metabolism, Uludag University Medical School, Bursa, Turkey; [2]Department of Internal Medicine, Uludag University Medical School, Bursa, Turkey; [3]Department of Endocrinology and Metabolism, Sevket Yilmaz Training and Research Hospital, Bursa, Turkey.

Introduction
Primary thyroid lymphomas are rare cancers and account 1–5% of all thyroid cancers and 3% of all extranodal non hodgkin lymphomas (NHLs). We aimed to present cases of thyroid lymphoma encountered in our clinic.
Case 1: A 54-year-old female patient admitted with pain and swallow on the cervical region. In ultrasonographic (USG) thyroid examination, it was found that both thyroid lobes were very large with routh parenchyme consistent with chronic thyroiditis; also there was a solid nodule 23 mm in diameter in left side. In fine-needle aspiration biopsy (FNAB) of thyroid, there were suspicious findings strongly indicating lymphoid hyperplasy. Patient underwent total thyroidectomy. Pathology results were consistent with extranodal (MALT type) marginal zone lymphoma. There were no pathologic findings implicating systemic involvement; patient is still followed-up.
Case 2: A 40-year-old female patient admitted with hypothyroidism. In USG examination of thyroid, it was found that thyroid parenchyme was extensively heterogeneous and there were multiple nodules. FNAB findings were reported as Hashimoto's thyroiditis and papillary carcinoma. Patient underwent total thyroidectomy and pathology results were considered as morphologic and immunephenotypic findings consistent with extranodal (MALT type) marginal zone lymphoma. Patient underwent radiotherapy. She is in remission and still followed-up.
Discussion
Primary thyroid lymphomas are rare cancers. Hashimoto's thyroiditis has been found 94% of the primary thyroid lymphoma cases. MALT lymphoma of thyroid has best prognosis with 100% of 5-year survival expectancy. Early diagnosis is important.

DOI: 10.1530/endoabs.37.EP997

EP998

Factors affecting the efficacy of radioiodine therapy in patients with Graves' disease

Magdalena Pogwizd, Agata Baldys-Waligorska, Dorota Pach, Monika Buziak-Bereza & Alicja Hubalewska-Dydejczyk
Department of Endocrinology, Medical College, Jagiellonian University, Krakow, Poland.

Introduction
In treating hyperthyroidism in Graves' disease (GD) patients with 131-iodine, the optimum activity of radioiodide is yet to be established. We analysed factors affecting the efficacy of ^{131}I radiotherapy in GD patients.
Materials and methods
The analysed group consisted of 362 (80.9% females and 19.1% males) GD patients, of median age 53 (min: 14 and max: 85) years. GD was diagnosed from clinical features, laboratory tests, thyroid USG, and scintigraphy. All patients with orbitopathy (GO) received glucocorticoids to prevent GO exacerbation. Focal lesions were observed in 164 (84% females and 16% males) patients. ^{131}I was applied for the first time in 85.4% of patients; 45.8% received ^{131}I more than once; 6.1% of all patients received it on first onset of hyperthyroidism, while 48.1% received it on first recurrence. The activity delivered was based on clinical

status, thyroid USG-established volume and 24-h ^{131}I uptake. Ranges of ^{131}I activity applied were: up to 555, 555–800, and above 800 MBq. Six months post ^{131}I treatment euthyroidism or hypothyroidism were stated in 72% of patients.
Results
The median thyroid volume was significantly larger in men (30 ml (18.95–52.75)) than in women (24 ml (16.1–37)) ($P=0.006$). No significant differences in efficacy related to ^{131}I activity applied were stated six months post treatment. In the group of patients treated with lower (<555 MBq) or higher (555–800 MBq) ^{131}I activity, 76 or 68.5% of patients, respectively, were effectively cured. Presence of focal lesions did not affect the efficacy of ^{131}I treatment either. In the group of 28 GO patients significant increase of hTRAB level was observed. *De novo* GO occurred in 1.9% of patients.
Conclusions
The efficacy of ^{131}I treatment in GD patients evaluated after 6 months was negatively affected by larger thyroid volumes and by anti-thyroid medication.

DOI: 10.1530/endoabs.37.EP998

EP999

Descriptive analysis of a series of 1567 thyroidectomies in Castilla La Mancha and its association with thyroid cancer

Enrique Castro[1], Sandra Herranz[5], Manuel Delgado[2], Dulce Calderón[4], Jose Joaquin Alfaro[3], Julia Sastre[1] & Florentino Del Val[1]
[1]Hospital Virgen de la Salud, Toledo, Spain; [2]Hospital General Ciudad Real, Ciudad Real, Spain; [3]Hospital General de Albacete, Albacete, Spain; [4]Hospital Virgen de la Luz, Cuenca, Spain; [5]Hospital Universitario, Guadalajara, Spain.

Introduction
We wanted to analyse the descriptive variables of a series of 1567 thyroidectomy patients between 2010 and 2013 and its association with malignancy in our series.
Material and methods
Retrospective, multicentre study done by review of the medical records of 1567 patients who became thyroidectomy between 2010 and 2013 in eight sanitary areas. This is an analysis of clinical and demographic variables.
Results
The percentage of women/men was 82%/18%. The mean age was 51.8 years (S.D. 15). For the following variables, median and IC range were: time tracking: 1 year (0–3); number of visits 3 (2–6); number of scans performed 1 (1–3); and cytological studies 1 (1–2). 60.9% of patients had a family history of thyroid disease. Thyroid cancer in the family: 3.3% of cases (52 patients). Goitre/nodule was incidental in 30.8% of cases. The reasons for surgical indications were: cytological findings (33.1%); size without compressive symptoms (26%), ultrasound findings (13.5%), compressive symptoms (11.9%); hyperthyroidism 11.6% (4.3% for Graves' disease); growth (9.9%) express wish of the patient (5.5%); lymphadenopathy (3.8%); hardness (1.1%); previous neck irradiation (0.4%); and recurrent nerve injury (0.3%).
Conclusions
In a multivariate analysis to predict malignancy were significant variables with OR: male sex 1.44 (1.023–2.05) ($P=0.037$); family history of thyroid cancer: 2.43 (1.23–4.8) ($P=0.010$); cytology as surgical indication 3.15 (2.29–4.33) ($P=0.000$); growth as an indication 2.1 (1.23–3.5) ($P=0.006$); non-existence of compressive symptoms 1.92 (1.13–3.29) ($P=0.017$); no size criterion as indication 1.66 (1.13–2.45) ($P=0.011$); no hyperthyroidism 4.06 (1.8–9) ($P=0.001$); and no incidental finding 1.46 (1.03–2.07) ($P=0.03$).

DOI: 10.1530/endoabs.37.EP999

EP1000

Incidence of autoimmune thyroid disorders following treatment with pegylated interferon therapy for HCV infection among Egyptian patients

Salah Eldin Shelbaya, Makboul Khaled Mahmoud, Mona Mohamed Abdelsalam, Zaki Doaa Zakaria & Manar Alshahawey Alsayed Ghazy
Faculty of Medicine, Ain Shams University, Cairo, Egypt.

Introduction
Egypt has an epidemic of HCV. Interferon (IFN) is the drug of choice for treatment induces autoimmune thyroiditis. The biochemical characteristic of the autoimmune thyroid disorder is the presence of autoantibodies against thyroid peroxidase and thyroglobulin. Chemokine ligand 10 (CXCL10) is an IFN inducible chemokine involved in the autoimmune thyroid disease.
Aim
To assess the incidence of autoimmune thyroid disorder following treatment with IFN and if we can predict its development.
Method
40 patients with chronic HCV participated and received IFN for 6 months. Liver function (ALT and AST), HCV–PCR, FT_3, FT_4, TSH, anti-thyroid peroxidase (ATPO) antibodies, anti-thyroglobulin antibodies, and CXCL10 all done before and after 6 months of treatment.
Results
At the end of the study, patients divided into three groups according to their response to IFN therapy and developing of thyroid dysfunction. Group A: 24 patients (60%) responded to Interferon and their liver enzymes and PCR turned normal without developing thyroid dysfunction. Group B: ten patients (25%) didn't respond to IFN and their liver enzymes and PCR still elevated, without developing thyroid dysfunction. Group C: six patients (15%) had elevated thyroid antibodies after 6 months of treatment, but responded to IFN and became PCR negative. At the beginning of the study: group C had higher ATPO ($P=0.06$) and ATG in comparison with A and B ($P=0.09$). The lowest level of PCR ($P\leq0.01$) and CXCL10 in comparison with A and B ($P\leq0.01$). After therapy: group C showed elevation of ATG ($P\leq0.01$), and ATPO level ($P\leq0.01$) in comparison with A and B. Groups A and C showed marked decrease in CXCL10 level in comparison with B ($P\leq0.01$).
Conclusion
15% of the participants developed thyroid dysfunction after IFN therapy. They had high normal level of thyroid antibodies and lower CXCL10 before treatment.

DOI: 10.1530/endoabs.37.EP1000

EP1001

Does vitamin D differ among the different thyroid states? A pilot study in Egyptian patients

Mohamed Fahmy Abdelaziz, Salwa Seddik Hosney, Mona Mohamed Abdelsalam, Alyaa Ahmed Alsherbeny & Yassmin Yehia Rashwan
Faculty of Medicine, Ain Shams University, Cairo, Egypt.

Introduction
Vitamin D plays an essential role in calcium homeostasis and bone metabolism, immune modulation, and control of other hormonal systems. Vitamin D deficiency is also common for many reasons. On the other hand, thyroid diseases have widespread systemic manifestations including their effect on bone metabolism.
Aim
To assess vitamin D status among Egyptian patients with different thyroid states: euthyroid, hypothyroid, or hyperthyroid states.
Subjects and method
45 participants (39 females and six males) were divided into three groups: Group 1: (15) euthyroid subject, group 2: (15) hyperthyroid subjects, and group 3: (15) hypothyroid subjects. Diseases and drugs that affect vitamin D were excluded. History taking including dietary habits, sun exposure and clothes and full examination was done. Serum 25-hydroxy vitamin D level by ELISA, ionised calcium, phosphorus, alkaline phosphatase, TSH, free T_3, and free T_4 were assessed.
Results
The study showed high incidence of vitamin D deficiency among all groups. 21 subjects (45.6%) had vitamin D deficiency (<30 nmol/l), 24 subjects (52.1%) had insufficiency (30–75 nmol/l), and one subject (2.7%) had vitamin D sufficiency. 25-hydroxy vitamin D was significantly different between groups with the level of 25 ± 15.78 nmol/l in group 1, 42.88 ± 20.03 nmol/l in group 2, and 28.46 ± 20.03 nmol/l ($P<0.05$). 60% in group 1, 50% in group 2, and 33.3% in group 3 had sufficient sun exposure with no significant difference between the three groups ($P=0.8$). Nearly 80% were veiled with no significant difference between the three groups ($P=0.2$). No difference between groups as regard sufficient dietary vitamin D ($P>0.05$). There was no significant difference between groups as regard serum ionised calcium and phosphorus and alkaline phosphatase ($P>0.05$).
Conclusion
Vitamin D was deficient in the different status of thyroid function. Assessment of vitamin D and replacement might be recommended in patient with thyroid disorder.

DOI: 10.1530/endoabs.37.EP1001

EP1002

Prevalence of thyroid dysfunction in Spain: diabetes study

Sergio Valdés[1], Cristina Maldonado-Araque[1], María José Tapia[1], Ana Lago[1], Vidal Perez-Valero[1], Albert Goday[2], Luis Castaño[3], Edelmiro Delgado[4], Joan Vendrell[5], Gemma Rojo-Martínez[1] & Federico Soriguer[1]
[1]Hospital Regional de Málaga, Málaga, Spain; [2]Hospital del Mar, Barcelona, Spain; [3]Hospital de Cruces, Baracaldo, Spain; [4]Hospital Central de Asturias, Oviedo, Spain; [5]Hospital Universitario Joan XXIII, Tarragona, Spain.

Introduction
Thyroid dysfunction is a common health problem. Its prevalence may vary in different populations, and in Spain, it has not been sufficiently studied. The aim of this study was to evaluate the prevalence of thyroid dysfunction (clinical and subclinical) in our country.
Materials and methods
The diabetes study is a national, cross-sectional, population-based survey. Target population: the entire Spanish population >18 years. Sample: >5000 subjects in 112 clusters. Participation: 57%. Variables: clinical, demographic, and lifestyle survey, physical examination and blood sampling. Study period: 2008–2010. Specific variables for this study: the concentration of TSH, FT_4, FT_3, and TPOab antibodies was determined by chemiluminescence (Roche) in 4530 subjects. Iodine concentration was measured in an isolated urine sample by the Benotti technique.
Results
The prevalence of treated hypothyroidism, untreated subclinical hypothyroidism and untreated clinical hypothyroidism were 4.2% (95% CI 3.6–4.9%), 4.6% (95% CI 4.0–5.2%), and 0.3% (95% CI 0.1–0.5%) respectively. The prevalence of hyperthyroidism was 0.8% (95% CI 0.6–1.1%) and the prevalence of positive thyroid autoimmunity (TPO >50 IU/ml) and 7.5% (95% CI 6.7–8.3%). All thyroid disorders were more prevalent in women than in men: hypothyroidism (total) 13.3% (12.0–14.6%) vs 4.8% (3.8–5.7%), hyperthyroidism 1.1% (0.7–1.4%) vs 0.6% (0.3–1.0%), and positive thyroid autoimmunity 10.8% (9.6–12.1%) vs 4.1% (3.2–5.0%) respectively. Hypothyroidism was associated with the presence of positive anti-TPO antibodies ($P<0.001$) and elevated urinary iodine levels ($P<0.001$).
Conclusions
We report for the first time the prevalence of thyroid dysfunction in a representative sample of the Spanish population.
Disclosure
CIBERDEM, Ministry of Health, Spanish Society of Diabetes. FIS PI11/02755. SAEN.
DOI: 10.1530/endoabs.37.EP1002

EP1003

Presentations and outcome of thyroiditis from an Outpatient Clinic of Endocrinology

Muhammad Shahid, Saeed Mahar & Shiraz Shaikh
Liaquat National Hospital, Karachi, Pakistan.

Background
Thyroiditis is 'the disorder in which there is inflammation of the thyroid gland'. If diagnosed earlier have often good chances of recovery. Limited data is available related to this problem from low income countries and hence there is delay in the diagnosis and management of this important disorder. The objective of the study was to assess the clinical presentations and early outcome of patients presenting with thyroiditis in a tertiary care hospital.
Design/methods
This case series was conducted from December 2013 to September 2014. Patients between 18 and 70 years of age with acute onset of thyroiditis confirmed on thyroid scan or clinical judgment in cases of contraindication of thyroid scan presenting to the out patient services was included in the study. Pregnant females, psychiatric illnesses, those patients having other chronic illnesses were excluded from the study. Patients were followed for 6 months.
Results
A total of 26 patients with thyroiditis attended the endocrine clinic. Mean age of patients was 41.2 ± 11.12 years. There were 18 (69.2%) females. Clinical presentations (signs) were fever (65.4%), tender neck (23.1%), goitre (19.2%), localised tenderness in neck, and palpable lymph nodes (26.9%). Major symptoms reported were sore throat (69.2%), weight loss (38.5%) whereas upper respiratory tract infection, thyroid pain, tremor, sweating and fever of unknown origin in 26.9% cases. All the patients had raised ESR. Low TSH <0.4 was seen in 88.5 and 57.7% had raised free T_4 >1.8. Complete recovery was seen in 88.5% patients while 11.5% had early hypothyroidism.
Conclusion
Fever and sore throat were the main presenting features of thyroiditis patients. ESR was raised in all patients. Majority of patients had complete recovery with appropriate management.
DOI: 10.1530/endoabs.37.EP1003

EP1004

Association between fibromyalgia and thyroid autoimmunity

Nooshin Shirzad[1,2], Shafieh Movassaghi[3], Hoda Karmostaji[3], Fatemeh Esfahanian[2], Mahboobeh Hemmatabadi[2] & Mostafa Qorbani[1]
[1]Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Endocrinology and Metabolism Research Institute, Tehran, Iran; [2]Endocrine Research Center, Valiasr Hospital, Tehran University of Medical Sciences, Tehran, Iran; [3]Rhomatology Research Center, Valiasr Hospital, Tehran University of Medical Sciences, Tehran, Iran.

Fibromyalgia is a disorder characterised by fatigue, generalised body pain and cognitive symptoms, and the aetiology has not been clearly described. Because similar symptoms are frequently found in Hashimoto's thyroiditis and there is not an optimal response to the treatment of hypothyroidism, the aim of this study is to determine the prevalence of fibromyalgia in patients with Hashimoto's thyroiditis, to explain the symptoms and to select the appropriate treatment. This cross-sectional study used the 'case study' method and included 100 euthyroid patients with Hashimoto's thyroiditis that were referred to the rheumatology clinic of Imam Khomeini hospital in 1392. Patients who met the inclusion criteria underwent a physical examination according to ACR 2010 criteria for fibromyalgia. Data collection and analysis was performed using SPSS 22 software. The mean age of the patients was 38.7 ± 11.58 years, and 7% of patients were male. The prevalence of fibromyalgia was 5%. No significant correlation was found between fibromyalgia patients and other variables such as age, gender, marital status, menopause, education, duration of Hashimoto's thyroiditis, Anti-TPO and TSH levels, and also no correlation was found between the severity of fibromyalgia and these variables. The prevalence of fibromyalgia was not higher than the normal population; thus, musculoskeletal symptoms could not be justified only with fibromyalgia. According to the low number of samples and lack of information on the prevalence of the disease in Iran, further studies using a larger population are recommended.
DOI: 10.1530/endoabs.37.EP1004

EP1005

A case report of Hoffmann's syndrome

Ziynet Alphan Uç[1] & Süheyla Gorar[2]
[1]Usak, Government Hospital, Usak, Turkey; [2]Antalya, Training and Research Hospital, Antalya, Turkey.

Introduction
Hoffman's syndrome is a rare form of hypothyroid myopathy characterised with muscle hypertrophy, stiffness and wakefulness.
Case report
A 43-years-old woman admitted to our hospital with a complaint of fatigue and progressive muscular weakness with cramps and myalgia started 3 months before.Thyroid gland examination was normal. On neurological examination she had proximal and lower limb muscle weakness(3/4) and hyporeflexia. Her calf muscles was hypertrophic.Laboratorial investigation reveals increased serum levels of muscular enzymes, dislipidemia severe hypothroidism. Electromyography (EMG) muscles revealed low amplitude and short duration motor unit action potentials (MUAPs) with early recruitment suggestive of a myopathic disorder. The patient was diagnosed of having severe hypothyroidism with Hoffman syndrome. L-thyroxine treatment was started (100 μg per day) and dose was elevated 150 μg per day after 2 weeks later. After 1 month therapy her hypothyroid symptoms reduced, pseudohypertrophy of the calf muscles regressed, muscle enzymes were reduced.
Discussion
The characteristic features of Hoffman's syndrome include localised or generalised hypertrophy of muscles in addition to muscle weakness, stiffness, cramps and pain as compared to the classic symptoms of hypothyroidism.The CPK is the best biochemical marker of myopaties. Mild to moderate elevation of serum CPK level is seen in 70–90% patients with hypothyroidism indicative

of muscle involvement but does not correlate with the severity of weakness. The clinical presentation and biochemical features might make it a bit difficult for the physician to differentiate it from polymyositis or muscle dystrophies. Hoffman Syndrome has good prognosis if diagnosed earlier and treated appropriately.This case report shows that Hoffman syndrome, though a rare presentation of hypothyroidism has a good prognosis with timely diagnosis and appropriate management. In the differential diagnosis of myopathy with pseudo-hypertrophy, Hoffmann's syndrome should be considered. It is an infrequent cause of myopathy, with good prognosis.

DOI: 10.1530/endoabs.37.EP1005

EP1006

Successful treatment with radiotherapy in a patient who developed severe Graves'-like ophthalmopathy after treatment with pegylated interferon Alpha-2a for hepatitis C

Carmen Acosta-Calero[1], Claudia Arnas-Leon[1], Ruth Carmona-Vigo[2], Francisco Javier Martinez-Martin[1] & Pedro Conrado Jimenez-Santana[3]
[1]Endocrinology Department, Hospital Universitario de Gran Canaria Dr. Negrin, Las Palmas de Gran Canaria, Spain; [2]Radiation Oncology Department, Hospital Universitario de Gran Canaria Dr. Negrin, Las Palmas de Gran Canaria, Spain; [3]Internal Medicine Department, Hospital Universitario de Gran Canaria Dr. Negrin, Las Palmas de Gran Canaria, Spain.

Introduction
Interferon treatment for hepatitis C has been associated with Graves'-like thyroiditis, developing in rare instances severe ophthalmopathy. The usual management is interferon withdrawal and high-dose corticosteroids, but it may interfere with the resolution of hepatitis. Hereby we report a case successfully treated with radiotherapy, which in our knowledge has never been previously reported.
Case report
A 52-year-old woman was diagnosed of chronic hepatitis C (serotype 1) and began treatment with pegylated Interferon Alpha-2A (Pegasys, 180 μg weekly) and ribavirin (1200 mg per day), After a year, she achieved clinical, biochemical and virological remission and the treatment was withdrawn. In the last month of antiviral treatment, the patient reported symptoms of hyperthyroidism, eyelid swelling and diplopia. TSH was suppressed and free T_4 was 2.27 ng/dl. Tc-99 m scintigraphy showed irregular uptake with cold areas. The ultrasonography showed multinodular goiter, and the FNAC was reported as chronic lymphocitic thyroiditis (benign). An orbitary CT scan showed prominent enlargement of muscle and retroorbitary fat with exophthalmos. The ophthalmologist recommended high-dose corticosteroid pulses, but we were concerned about the risk of hepatitis recurrence. The patient received standard metimazol treatment for hyperthyroidism and bilateral retro-orbital irradiation with a total dose of 10 Gy fractionated in 1 Gy once a week over 10 weeks. After the seventh session, the diplopia remitted and the patient is presently asymptomatic.
Conclusions
Retroorbitary radiotherapy should be considered as an alternative treatment for Graves'-like ophthalmopathy associated to interferon treatment, avoiding the need for high-dose corticosteroids which may result in hepatitis recurrence.

DOI: 10.1530/endoabs.37.EP1006

EP1007

Hypothyroidism in clinical practice

Faiza Qari
Kauh, Jeddah, Saudi Arabia.

Hypothyroidism is the most common endocrine disease that was seen in the clinical practice especially for family. What issues about hypothyroidism should be covered in clinical practice? A 36-year-old woman who was diagnosed with hypothyroidism 3 years ago tells her endocrinologist that she wants to conceive in the next year. She was treated with LT_4, 0.1 mg per day. Her last serum TSH was 0.7 mIU/l. She is instructed to notify her endocrinologist as soon as she finds out that she is pregnant so that a serum TSH level can be checked. Her menstrual period is 1 week late, a home pregnancy test is positive, and her serum. TSH level is 1.9 mIU/l.
Conclusions
The clinical issues were addressed by clinical scenario followed by questions and stressed on the important clinical points.

DOI: 10.1530/endoabs.37.EP1007

EP1008

Graves' disease with autoimmune haemolytic anemia

Randa Salam, Nagwa Ramadan & Fatma Gaber
Cairo University, Cairo, Egypt.

Introduction
Haematologic involvement is not uncommon in Graves' disease. Autoimmune haemolytic anaemia is occasionally reported in patients with other autoimmune illnesses. However very rarely reported in Graves' disease.
Case report
We report a 19-year-old female with reactive arthritis, Graves' disease and autoimmune haemolytic anaemia while under treatment with methimazole. Physical examination: Under built female BMI 17, Blood pressure was 110/70, heart rate 100 min., respiratory rate 16 min, temperature 37.6, jaundice, pallor, no cervical, supraclavicular, epitrochlear, axillary, or inguinal lymphadenopathy. The thyroid gland mildly enlarged not nodular no thrill or bruit, proptosis, no lid-lag, or tremor. Lungs were clear and the heart rhythm was regular, accentuated S1, pulmonary component of S2 ejection systolic murmur over the cardiac base no click, or gallop. The abdomen was soft and non-tender, with the liver edge not palpable; the spleen was palpable 3 cm below LF costal margin, joint pain affecting both knees with limitation of movement.
Investigations
Haemoglobin 4.4 g/dl, MCV 107.2, platelet count 193 000, WBC count 4 000, reticulocyte count 23.3%, Bilirubin 4.0 mg/dl (direct 0.4), LDH 311 U/l, positive comb test, ESR;128, ANA negative. Abdominal sonar mild splenomegaly, normal echo cardiography. The patient was started on prednisone 1 mg/kg with rapid improvement in her anaemia and jaundice. 11 days after admission haemoglobin improved to 10.0 g/dl. The prednisone was tapered off over 3 months with continued stable haemoglobin levels and no evidence of recurrent haemolysis.
Conclusion
We report a case of concurrent reactive arthritis, Graves' disease, and autoimmune haemolytic anaemia. Yersinia enterocolitica infection could theoretically cause both reactive arthritis and Graves' disease, although we cannot prove this connection in our patient's case which improved dramatically on steroids.

DOI: 10.1530/endoabs.37.EP1008

EP1009

Successful treatment of hypothyroidism with rectal thyroxine can be achieved with variable dose response: a case report

Muhammad Naeem Durrani, Najmul Islam, Nanik Ram & sarwar Malik
Aga Khan University Hospital, Karachi, Pakistan.

Introduction
Hypothyroidism is a common endocrine disorder worldwide. Its treatment is with oral thyroxine, but when this route cannot be utilised then intravenous thyroxine is an alternate but not available in some countries so rectal thyroxine administration can be used but clinical experience is lacking.
Case report
This is a case of a 55-years-old Pakistani male known case of hypothyroidism since July 2007 and was maintaining normal TSH and FT_4 level on thyroxine 125 μg per day. He was diagnosed as recurrent laryngeal carcinoma and planned to undergo change of tracheostomy and feeding gastrojejunostomy surgery. As he was unable to take oral referred for hypothyroid medical optimisation prior to surgery. On presentation he was constipated, lethargic had tracheostomy and was on total parental nutrition and not taking his thyroxine for last one month. His TSH was >150uIU/ml and FT_4 was 0.44 ng/dl. As the intravenous thyroxin was not available was started on rectal suppository of thyroxin 250 μg per day. The dose of rectal thyroxine gradually increased to 500 μg per day and his TSH level dropped to 8.83 uIU/ml and FT_4 level raised to 1.29 ng/dl and patient underwent successfully for gastrojejustomy and started him on thyroxine 125 mcg per day through gastrojeunostmy tube and maintaining normal TSH and FT_4 level.
Conclusion
Patients with hypothyroidism can be managed with rectal thyroxine responses are variable as in our case required four times the oral dose.

DOI: 10.1530/endoabs.37.EP1009

EP1010

1 year response rate to 10 mCi radioactive iodine (I131) in patients with relapsed Graves' disease

Khaled Salman[1], Safwan Zatary[2], Shereen Wagieh[3], Tarek Munshy[1], Maha Abd-El Kareem[4], Yasser Mohammad[4] & Manal Al-Ezzi[3]
[1]Nuclear Medicine Deparmetnt, King Abdulla medical City (KAMC), Mekka, Saudi Arabia; [2]Endocrinology Department, King Abdulla medical City (KAMC), Mekka, Saudi Arabia; [3]Nuclear Medicine Department, King Abdulla Medical City (KAMC), Jeddah, Saudi Arabia; [4]Nuclear Medicine Department, Cairo University Hospitals, Cairo, Egypt

Introduction
Failure of medical treatment in patients with primary diffuse toxic goitre (Graves'disease) was reported in around 50% of patients and can occur few months after cessation of therapy. Radioactive I131 therapy is a good therapeutic alternative that can be used safely in patients with relapsed Graves' disease and achieve good response rate with hypothyroisdism representing the main side effect.
Aim
The aim of the current study is to asses one year response rate to 10 mCi of I131 in patients with relapsed Graves' disease post failure of medical treatment patients and methods: 33 patients who had transient control of clinical manifestations with normal thyroid hormonal profile post at least 12 months of continuous proper dose of of neomercazole therapy were included. This was followed by variable period of disease control (range: 7–19 months). After a mean period of 13.4 ± 5.5 months with no thyrotoxic clinical manifestations and more importantly normal thyroid hormonal profile during follow up, all patients had clinically and biochemically confirmed thyrotoxic state with a diagnosis of relapsed primary diffuse toxic goiter (relapsed Graves' disease). All presented for I131 therapy post failure of medical treatment and confirmed relapse. They received 10 mCi of I131 on out patient basis. Patients were followed up for 1 year to assess response to I131 therapy.
Results
14 patients (40.4%) developed clinical hypothyroidism that was confirmed biochemically 3 months post I131 therapy. 1 year post 10 mCi of I131 both clinical and biochemical data showed overt hypothyroid state in 21 patients (63.6%). One patient (3%) with subclinical hypothyroidism was diagnosed by thyroid function tests with no clinical symptoms. Normal thyroid function tests with no clinical manifestations of recurrence were reported in eight patients (24.4%). Considering both hypothyroid and euthyroid states as successful response to I131 therapy, so the overall successful response rate post 1 year of 10 mCi of I131 therapy is 91%. Failure of response to 10 mCi of I131 with a need for a second I131 dose was reported in only three patients (9%).
Conclusion
10 mCi of I131 is a good therapeutic choice in patients with relapsed Graves' disease with an overall response rate 1 year post I131 therapy of 91%. Hypothyroidism occurs as early as 3 months post therapy in around 40% of patients, increasing to 66.6% by the end of first year after therapy.

DOI: 10.1530/endoabs.37.EP1010

EP1011

Correlation of midkine levels in serum and thyroid nodules with histopathological, haematological and radiological variables

Fatih Kuzu[1,2], Dilek Arpaci[1,2], Ayfer Altas[2], Gürkan Haytaoglu[2], Murat Can[3], Figen Barut[4,5] & Taner Bayraktaroglu[1,2]
[1]Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology and Metabolism, Bulent Ecevit University, Zonguldak, Turkey; [2]Faculty of Medicine, Department of Internal Medicine, Bulent Ecevit University, Zonguldak, Turkey; [3]Faculty of Medicine, Department of Biochemistry, Bulent Ecevit University, Zonguldak, Turkey; [4]Faculty of Medicine, Department of Pathology, Bulent Ecevit University, Zonguldak, Turkey; [5]Faculty of Medicine, Department of Biostatistics, Bulent Ecevit University, Zonguldak, Turkey.

Aim
To evaluate serum (SMK) and nodular (NMK) midkine levels in thyroid nodules and explore its relevance to ultrasound feature/pathological results.
Methods
A total of 80 patients (56 women, 24 men) with thyroid nodules were included in this prospective study. Hemograms, thyroid function tests, fine needle aspiration biopsies, ultrasonographic evaluation were routinely made. In addition, levels of SMK and NMK were measured. Any possible correlations between SMK, NMK and biochemical or radiological variables under investigation were sought.
Results
The average age of study group was 51.9 ± 14.4. Both SMK and NMK were found to be higher in hypoechoic nodules with an irregular border and absent halo. Serum MK levels were significantly higher in nodules containing microcalcifications than the macrocalcification or without calcification ($P = 0.001$). Serum MK levels were high in patients with differentiated thyroid carcinoma, compared to patients with follicular adenoma or nodular hyperplasia. Serum MK levels seemed to correlate with nodular MK levels ($r = 0.54$, $P < 0.001$).
Conclusion
Results of the current study showed that both SMK and NMK were indicators of highly malignant/suspicious thyroid cytopathology and also correlate well with sonographic features of thyroid malignancy. We suggest that Midkine may serve as a novel biomarker in conjunction with the cytopathological results in preoperative assessment of thyroid nodules.

DOI: 10.1530/endoabs.37.EP1011

EP1012

Correlation of VEGF, VEGFR-1 levels in serum and thyroid nodules with histopathological and radiological variables

Gurkan Haytaoglu[1,2], Dilek Arpaci[1,2], Fatih Kuzu[1,2], Ayfer Altas[1], Murat Can[3], Figen Barut[4], Firuzan Kokturk[5], Sevil Uygun Ilikhan[1] & Taner Bayraktaroglu[1,2]
[1]Department of Medicine, Department of Internal Medicine, Bulent Ecevit University, Zonguldak, Turkey; [2]Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology and Metabolism, Bulent Ecevit University, Zonguldak, Turkey; [3]Faculty of Medicine, Department of Biochemistry, Bulent Ecevit University, Zonguldak, Turkey; [4]Faculty of Medicine, Department of Pathology, Bulent Ecevit University, Zonguldak, Turkey; [5]Faculty of Medicine, Department of Bioistatistics, Bulent Ecevit University, Zonguldak, Turkey.

Aim
To evaluate serum and intranodular vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor-1 (VEGFR-1) level thyroid nodules and explore its relevance to ultrasound feature/pathological results.
Methods
A total of 80 patients (62 women and 18 men) with thyroid nodules were included in this prospective study. Thyroid function tests, fine needle aspiration biopsies, ultrasonographic and scintigraphic evaluation were routinely made. In addition, levels of serum and intranodular VEGF, VEGFR-1 were measured. Any possible correlations between serum and intranodular VEGF, VEGFR-1 and biochemical or radiological variables under investigation were sought.
Results
The average age of study group was 54.1 ± 13.3. Average BMI was 27.6 ± 4.2 kg/m^2. There were no statistically significant differences between sVEGF; nVEGF; nVEGFR-1 based on gender ($P > 0.005$). But serum VEGFR-1 in male was higher than women ($P = 0.045$). Although nVEGFR-1 was significantly higher in normal BMI patients compared with the obese patients; ($P = 0.02$); there were no differences sVEGF, sVEGFR-1 and nVEGFR-1. There were no significant differences between sVEGF; nVEGFR-1; sVEGFR-1 and nVEGFR-1 levels ($P > 0.05$) according to number of nodules (single and multinodular), benign and malignant ultrasonographic features (large nodules >4 cm; microcalcifications; intranodular hypervascularity; irregular border; hypoechoic structure; incomplete thick halo; regional lympadenopathy). When we grouped patients according to the thyroid status; sVEGFR-1 and nVEGFR-1 levels were higher in hyperthyroid patients than euthyroid patient ($P < 0.05$ and $P = 0.003$). In addition, nVEGFR-1 level was higher in hypothyroid patient than thyroid patients. ($P = 0.016$). There were no significant differences sVEGFR-1; nVEGFR-1 and nVEGF levels between the groups according to scintigraphic sign. But sVEGF was found higher in hyperactive nodules than others. sVEGF, sVEGFR 1, nVEGF, nVEGFR1 levels had no significant differences according to thyroid nodule size; ($P > 0.05$). There were no significant differences between sVEGF; sVEGFR-1; nVEGF and nVEGFR-1 levels between malignant/suspicious cytology and benign cytology ($P > 0.05$). Both sVEGFR-1($r = 0.29$; $P = 0.008$) and nVEGF levels inside nodule ($r = 0.29$; $P = 0.01$). Was significantly raised with increasing age. nVEGFR-1 was decreased with increasing BMI ($r = -0.32$; $P = 0.004$). There was no relationship between nodule size and sVEGF; nVEGF; sVEGFR1; nVEGFR1 ($P > 0.05$).
Conclusion
As a result; in our study we showed a relationship between sVEGF; nVEGF; sVEGFR-1; nVEGFR1 levels; and age; gender; BMI; hyperthyroidism. The number of malignant or suspicious groups were very small in our study, which is the limitation of this study. Studies which has more number of patients are required to evaluate it.

DOI: 10.1530/endoabs.37.EP1012

EP1013

Iodine nutrition status among neonates in Uttarakhand, India (for ESE Young Investigator Award)

Neha Sareen[1,2], Umesh Kapil[2] & Vanisha S Nambiar[1]
[1]Department of Foods and Nutrition, The Maharaja Sayajirao University of Baroda, Vadodara, India; [2]Department of Human Nutrition, All India Institute of Medical Sciences, New Delhi, India.

Introduction
Iodine deficiency (ID) is an endemic health problem in Uttarakhand State. ID leads to mental retardation, deaf mutism, squint, dwarfism, spastic diplegia, neurological defects and congenital anomalies. Iodine nutrition status amongst neonates can be assessed by estimating thyroid stimulating hormone (TSH).
Objectives
Current study aimed to assess iodine nutrition status among Neonates in Uttarakhand, India, a known endemic region for ID.
Methodology
Three districts, namely Udham Singh Nagar (USN), Nainital (N) and Pauri Garhwal (PG), were selected. In each district, all Hospitals/CHCs catering to the population for obstetric services were identified and enlisted. Six hospitals per district were selected keeping in view of operational feasibility. The 450 births occurring in these Hospitals/CHCs during the 12 months of study period were included for estimation of TSH. Total of 2013 neonates (649 from Udham Singh Nagar, 670 from Nainital and 694 from Pauri Garhwal) were studied. Umbilical cord blood samples of neonates were collected on filter paper and analyzed for TSH by sandwich enzyme-linked immunosorbent assay. WHO (2007) reported that a $<3\%$ frequency of TSH concentrations above 5 mIU/l in samples collected 3–4 days after birth indicates iodine sufficiency in a population.
Results
We found that 55.3% (USN), 76.4% (N) and 72.8% (PG) of the neonates had TSH levels of more than 5 mlU/l, thus indicating ID in the population studied. No statistically significant difference of gender on the TSH levels was observed.
Conclusion
Iodine deficiency continues to be a public health problem in Uttarakhand, India.
Disclosure
Indian Council of Medical Research, New Delhi (vide letter No: 5/9/1025/201 1-RHN).

DOI: 10.1530/endoabs.37.EP1013

EP1014

Prevalence of short stature in juvenile hypothyroidism and the impact of treatment in tertiary care centre

Sukriti Kumar[1] & Manish Gutch[2]
[1]SGPGI, Lucknow, India; [2]LLRM Medicalcollege, Meerut, India.

Background
Juvenile hypothyroidism is very common problem in developing part of world, and produces various skeletal manifestations and one of them is short stature and it is the most common reason for referral to endocrinologist. It has very wide etiology and one of them is hypothyroidism, which needs special attention, as the treatment impact of thyroxin replacement has favourable outcome.
Aim and objectives
To study the prevalence of juvenile hypothyroidism, to study the various radiological manifestation of juvenile hypothyroidism and to study the impact of treatment on short stature.
Materials and methods
Out of total 900 patients, 87 patients found to be of juvenile hypothyroidism were enrolled in the study that were 6–18 years of age with newly diagnosed or on follow in the OPD of Department of Endocrinology and Metabolism over a period of $1\frac{1}{2}$ years were evaluated clinically and by laboratory tests. Serial assays of TSH, T_4, T_3 and skeletal X-rays were done and clinical and radiological outcome of patients were analysed.
Statistical analysis
Data were analysed by SPSS version 17 and were presented in the values of mean, median, and percentages. The P-value of <0.05 was considered significant.
Results
The mean age of diagnosis of juvenile hypothyroidism was 11.2 years, and the females had twice the incidence than that of males, the mean TSH value were 118 μIU/ml while T_4 and T_3 were very low. Marked improvement in the anthropometry was seen in comparison to the initial assessment which was well correlated with the normalisation of the TSH level and the X-ray of the bone. The maximum impact of hypothyroidism was on delayed bone age.
Conclusion
Juvenile hypothyroidism, constituent about 10% of total hypothyroid patients and it is more common than congenital hypothyroidism. The presentations may be varied including short stature, spondylolisthesis, delayed bone age and irregular ossification of the epiphyses. Prompt recognition of the findings can lead to early and effective treatment, and improving the skeletal defects.

DOI: 10.1530/endoabs.37.EP1014

EP1015

The role of circulating sTWEAK in the pathogenesis of Hashimoto's thyroiditis and its relationship with other cytokines: a pilot study

Mustafa Altay[1], İhsan Ateş[2], Fatma Meriç Yılmaz[3], Canan Topçuoğlu[3], Mustafa Kaplan[4] & Fatma Aybala Altay[5]
[1]Department of Endocrinology and Metabolism, Keçiören Education and Research Hospital, Ankara, Turkey; [2]Department of Internal Medicine, Numune Education and Research Hospital, Ankara, Turkey; [3]Department of Biochemistry, Ankara, Numune Education and Research Hospital, Turkey; [4]Department of Gastroenterology, Yüksek ihtisas Education and Resarch Hospital, Ankara, Turkey; [5]Dışkapı Education and Research Hospital, Ankara, Turkey.

Objective
We aimed to investigate the role of sTWEAK in the pathogenesis of Hashimoto's Thyroiditis (HT) and its relationship with IL-12, IL 17-A and TGF-β1.
Methods
Serum TSH, FT_4, anti-TG and anti-TPO were measured and thyroid USG was performed to both group. In addition serum samples were collected and sTWEAK, IL 17-A, IL-12 and TGF-β1 were measured.
Patients
Six patients (20 patients were euthyroid, 20 patients were subclinical hypothyroidism and other 20 were overt hypothyroidism), who were newly diagnosed with HT and did not receive any treatment, and 20 patients with no known disease as the healthy control group were included in the study.
Results
The HT group had lower levels of sTWEAK and TGF-β1, but had higher levels of IL-12 and IL 17-A as compared to the control group. Of these, only the difference between IL 17-A levels reached the statistical significance (2.1 (1.1–10.7) vs 1.8 (1.2–2.3)) $P<0.001$). The overt hypothyroidism group had significantly higher levels of IL-12 than those of other groups. All of the subgroups had significantly higher levels of IL 17-A than those of control group. sTWEAK was negatively correlated with IL 17-A in the overt hypothyroidism.
Conclusions
We achieved data that support the role of IL-12 and IL17-A in the pathogenesis of HT but did not find significant differences between the sTWEAK level and the groups. Also, no significant relationship was identified between the sTWEAK level and either the thyroid autoantibodies or the cytokine levels of other pathways. Further studies are needed to present the effect of sTWEAK level on the autoimmune diseases.

DOI: 10.1530/endoabs.37.EP1015

EP1016

Serum selenium levels in euthyroid nodular thyroid diseases

Davut Sakiz[1], Ahmet Kaya[2] & Mustafa Kulaksizoglu[2]
[1]Necmettin Erbakan University Meram Medical Faculty Internal Medicine, Konya, Turkey; [2]Department of Endocrinology and Metabolism, Necmettin Erbakan University Meram Medical Faculty, Konya, Turkey.

Introduction
Thyroid gland is susceptible for nodulation. It is not clear which mechanism is responsible for the growth of only some follicular cells resulting in nodule formation. Selenium deficiency may a risk factor in the development of thyroid nodules. The aim of this study was to investigate the relationship between selenium levels in patients with euthyroid nodular thyroid diseases.
Design
Euthyroid 70 patients with solitary thyroid nodule, euthyroid 70 patients with more than one nodule healthy 60 patients without thyroid nodule were included in the study. Venous serum samples were stored at -80 °C and studied at the same day by spectrometric method.
Results
Selenium levels of patients with multiple thyroid nodules, solitary nodules and patients without nodules respectively were 57.3 ± 1.76 μg/l; 58.7 ± 1.80 μg/l and 57.6 ± 1.71 μg/l. The mean serum selenium level of all patients included in the study was 57.92 ± 14.43 μg/l. Serum selenium levels were minimally higher in men, although statistically significant difference was not observed. In our study,

significant relationship between serum selenium levels and nodular thyroid disease was not seen.
Conclusion
Our study was done in a iodine sufficient area. Mean serum selenium levels were lower compared to other studies in Turkey. This condition can be associated with the low selenium content of the soil. Nodular thyroid disease shows multifactorial features. Besides iodine deficiency additional factors such as selenium deficiency can be responsible for the increase of nodule formation. Further studies should be done to assess the role of selenium in the thyroid nodule formation.

DOI: 10.1530/endoabs.37.EP1016

EP1017

Technique of story-telling in Patient care with reference to endocrine surgery

Sabaretnam Mayilvaganan, Naval Bansal & Saroj Mishra
Sanjay Gandhi Postgraduate Institute of Medical sciences, Lucknow, India.

Background
In the modern day busy clinical practice the communication between patient/relative and care giver is at minimal level. The patients and relatives feel apprehensive when advised about the surgical/interventional treatment. In such situation they feel the need of detail information from the care givers which on many occasions is not available. Story telling is such a technique of health communication made out in common man language which can be made animated and interactive using virtual characters and can operate in a virtual environment eliminating the need of health professionals. We intended to study the efficacy of storytelling technique on patients undergoing Hemithyroidectomy for benign cytology.
Methods
A story of a lady (cartoon version) aged 25 years with a benign thyroid nodule who underwent uneventful Hemithyroidectomy is depicted in this movie including the history, clinical examination, investigations, counseling and the operative procedure and the running time of the animation movie is four minutes. For developing this movie, high end graphic computer work station and various multimedia authoring tools like Adobe Flash, Photoshop, Captivate, Maya and Final Cut Pro were used. The story was shown to patients with clinically solitary thyroid nodules who were provisional candidates for surgery in the outpatient department.The patients filled in the evaluation of Multimedia animation questionnaire at the time of discharge.
Result
20 patients filled the questionnaire. 19 found the movie useful and their remaining questionnaire was analyzed. Mean age was 35.45 ± 12.8 years.15 (75%) were females. All patients were euthyroid. The mean weight was 40.80 ± 20.79 gm. The final histopathology was colloid in majority. In the questionnaire, the mean score for improved understanding of the disease was 73.9 ± 14.7 ($P=0.003$), better organization of treatment was 78.6 ± 13.1 ($P=0.000$), stimulated interest in the relatives was 70.8 ± 15.8 and saved unnecessary discussion with the consultant was 55.5 ± 7.8.
Conclusion
Story telling is a useful tool in health communication. With widespread availability of high speed internet and affordable mobile computing devices such kind of information can be of use to the patients and relatives in decision making and also saves valuable time of the treating consultant. Future studies with larger numbers are needed.

DOI: 10.1530/endoabs.37.EP1017

EP1018

Adiponectin and gut hormones in thyroid dysfunction: a new concept (PFG axis)

S Ali Emami[1], Mehdi Hedayati[1] & M Reza Nazem[2]
[1]Cellular & Molecular Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [2]Department of Clinical Biochemistry, School of Medicine Tarbiat Modares University, Tehran, Iran.

Background
Integration between fat tissue, gastrointestinal tract, and the brain has attracted scientific interest in recent years. Thyroid hormones influence carbohydrate mechanisms *via* its interaction with adipocytokines and gut hormones. *Adiponectin*, *ghrelin* and *obestatin* play important roles in metabolism regulation. TSH receptors have been reported to be present in adipose tissue. Moreover, gut peptides signal to their functional cognate receptors on adipocytes. Nonetheless, the limited number of studies assessing the link between thyroid, gut hormones and adipokines have yielded conflicting results.
Aim
The objective of this study was to examine the associations between adiponectin, ghrelin and obestatin in patients with thyroid dysfunction. Furthermore, there might be a cross talk between them.
Methods
This study was performed on 72 subclinical hypo- and hyperthyroids, and 33 healthy euthyroid subjects. Serum concentrations of adiponectin, ghrelin, obestatin, TSH, free T_3 and free T_4 were measured by ELISA, ECLIA, IRMA and RIA methods.
Results
Serum levels of adiponectin were decreased in hypothyroids and increased in hyperthyroids (11.91 ± 5.02 and 15.13 ± 5.88 ng/ml, respectively) than the controls (12.73 ± 5.19 ng/ml, $P<0.05$). Ghrelin and obestatin values were lower in hypothyroids (320 ± 81 and 44.3 ± 11.7 ng/l respectively), and higher in hyperthyroids (750 ± 289 and 71.1 ± 27.3ng/l, respectively), compared to the controls (487 ± 110 and 58.5 ± 10.3 ng/l respectively, $P<0.05$). We found a negative correlation between TSH and adiponectin ($r=-0.42$, $P<0.05$). In addition, ghrelin and obestatin showed strong correlations with TSH ($r_{gr}=-0.53$, $r_{ob}=-0.59$; $P<0.001$). Also, strong correlations were observed between adiponetin and gut hormones ($r_{gr}=0.75$, $r_{ob}=0.69$; $P<0.001$).
Conclusion
Our findings show adiponectin and gut hormones are significantly affected by thyroid dysfunction. Additionally, these hormones are noticeably correlated with each other. Hence, we would like to consider a new regulatory concept, as a novel axis (*Pituitary-Fat-Gut axis*).

DOI: 10.1530/endoabs.37.EP1018

EP1019

A case of unilateral Graves' disease

Baris Cansu, Bengur Taskiran & Tatiana Bahceci
Yunusemre State Hospital, Eskisehir, Turkey.

Introduction
Thyroid hemiagenesis is a congenital developmental disorder. Most cases are euthyroid although hyperthyroidism, hypothyroidism, and malignancy may develop. We present a case of hemiagenesis with Graves' disease.
Case
A 45-year-old female patient was admitted to the endocrinology ward due to nausea and diarrhoea. She had hyperthyroidism for 1 year. She did not have any family member with thyroid disease. She was already on propylthiouracil therapy. She did not bear signs of Graves ophthalmopathy. Thyroid function tests revealed a TSH level of 0.01 μU/ml (0.35–4.94), free T_4 1.80 ng/dl (0.7–1.48), free T_3 3.82 pg/ml (1.71–3.71). TSH receptor antibody, antithyroid peroxidase antibody, and anti-thyroglobulin antibody were all positive. Left lobe and isthmus were invisible on ultrasound. Right lobe was $44 \times 18 \times 12$ mm in size with heterogenous hypervascular paranchyme echogenicity containing no nodules. Thyroid scan using 5 mCi ^{99m}Tc showed increased homogenous tracer uptake in the right lobe (6.7%). Isthmus, pyramidal lobe, and left lobe were not visualised. The patient was diagnosed with thyroid hemiagenesis and Graves' disease. The dose was readjusted and RAI therapy was planned.
Conclusion
In case of unilateral increased uptake on scintiscan Graves' disease with hemiagenesis must be kept in mind in the differential diagnosis of autonomus solitary adenoma, postinflammatory atrophy of thyroid in Hashimoto's disease, focal or unilateral subacute thyroiditis, and primary or metastatic carcinoma. It is prudent to do thyroid ultrasound along with scintigram.

DOI: 10.1530/endoabs.37.EP1019

EP1020

Evaluation of oxidative stress in patients with euthyroidism and with subclinical hypothyroidism

Şati Sena Yildiz, Sibel Serin, Gülçin Güngör Olçüm & Sema Basat
Ümraniye Research and Education Hospital, Istanbul, Turkey.

Objective
There is not sufficient data about oxidative stress in euthyroid Hashimoto (EH) and subclinical hypothyroid Hashimoto (SHH) disease. We studied oxidative stress with more oxidative stress tests in EH and SHH patients and assessed whether there is an association betweeen Hashimoto disease and PON1 phenotype.
Materials and method
35 EH and SHH patients and 38 control was included to the study. Comprehensive biochemistry, routine blood analysis, total antioxidant status (TAS), total oxidant status (TOS), oxidative stress index (OSI), arilesterase (ARE) paraxonase (PON), lipid hidroperoxide (LOOHs) were measured, and PON1 phenotype was determined.
Results
The levels of TOS and OSI increased significantly in patients with EH and SHH when compared with the control group (for TOS $P=0.005$, $P=0.004$; for OSI $P=<0.001$, $P=<0.001$, respectively). The level of ARE activity increased closely significant in patients with EH, and increase significantly in patients SSH patients when compared with the control group ($P=0.059$, $P=0.024$ respectively). The levels of PON, TAS, LOOHs are similar in the control group. Hashimoto's patients also have found that PON1 phenotype distribution similar to the control group (P: 0.303).
Conclusion
TOS, OSI and ARE were found to be increased in EH patients; however TAS, paraoxonase and LOOHs were similar to the control group. Increased OSI is related to increase in TOS in Hashimoto patients, because TAS was found to be similar to the controls. In EH and SHH patients, ARE activity, which is an indicator of molecular concentration of PON 1 enzyme, was found to be increased. On the other hand paraoxonase activity was similar to the control group, due to its consumption during the process of reducing the elevated LOOHs as a result of the increase in TOS. Consequently lipid peroxidation was found to be at a similar level with the controls. Oxidative stress parameters and biochemical values are similar in EH and SHH patients. In the PON1 phenotyping we performed, no PON1 phenotype creating predisposition to Hashimoto disease was detected.

DOI: 10.1530/endoabs.37.EP1020

EP1021

Circulating levels of irisin is elevated in patients suffering from hypothyroidism and obesity in Hashimoto's thyroiditis: original article

İhsan Ates[1], Mustafa Altay[1], Canan Topçuoğlu[2], F Meriç Yılmaz[2] & Guvenç Toprak[1]
[1]Department of Internal Medicine, Ankara Numune Education and Research Hospital, Ankara, Turkey; [2]Department of Biochemistry, Ankara Numune Education and Research Hospital, Ankara, Turkey.

Background and objectives
Our objective in this study was to discover the relationship of irisin hormone, which acts on adipose tissue and the metabolism as thyroid hormones, with the thyroid functions and the obesity secondary to thyroid disease.
Methods
A total of 74 patients were included in the study, of the patients, 37 were newly diagnosed with Hashimoto's thyroiditis dependent hypothyroidism but not received a treatment yet, and the remaining 37 were healthy volunteers with no known disease. Serum TSH, free thyroxin (fT_4), anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase (anti-TPO) were measured and thyroid ultrasonography was performed to both group. The serum irisin levels were measured using the commercially available ELISA kit.
Results
The hypothyroidism group had higher levels of irisin compared with the control group (2.77 ng/ml vs 2.15 ng/ml respectively; $P=0.017$). The hypothyroidism group had higher median levels of irisin in the obese patients than those in the control group (3.10 ng/ml vs 2.10 ng/ml relatively; $P=0.013$). The irisin level was negatively correlated with the age in the entire population and patients with hypothyroidism (r: -0.255, $P=0.028$; $r=-0.346$, $P=0.036$ respectively). The irisin level was positively correlated with the TSH ($r=0.247$, $P=0.034$) but negatively with the fT_4 ($r=-0.316$, $P=0.006$) in the entire population. Obesity, fT_4 and irisin level were identified to be independent predictors in the diagnosis of hypothyroidism in the multivariable logistic regression analysis.
Conclusions
To the best our knowledge, this study is the first in literature to identify that obesity, irisin level and fT_4 level are independent risk factors on hypothyroidism.

DOI: 10.1530/endoabs.37.EP1021

EP1022

The serum irisin level in non-diabetic patients with chronic kidney disease

İhsan Ates[1], Nihal Ozkayar[1], Canan Topçuoğlu[2] & Fatih Dede[1]
[1]Department of Interna Medicine, Ankara Numune Education and Research Hospital, Ankara, Turkey; [2]Department of Biochemistry, Ankara Numune Education and Research Hospital, Ankara, Turkey.

Background and objectives
Our objective in this study was to discover the relationship of irisin hormone, which acts on adipose tissue and the metabolism as thyroid hormones, with the thyroid functions and the obesity secondary to thyroid disease.
Methods
A total of 74 patients were included in the study, of the patients, 37 were newly diagnosed with Hashimoto's thyroiditis dependent hypothyroidism but not received a treatment yet, and the remaining 37 were healthy volunteers with no known disease. Serum TSH, free thyroxin (fT_4), anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase (anti-TPO) were measured and thyroid ultrasonography was performed to both group. The serum irisin levels were measured using the commercially available ELISA kit.
Results
The hypothyroidism group had higher levels of irisin compared with the control group (2.77 ng/ml vs 2.15 ng/ml respectively; $P=0.017$). The hypothyroidism group had higher median levels of irisin in the obese patients than those in the control group (3.10 ng/ml vs 2.10 ng/ml relatively; $P=0.013$). The irisin level was negatively correlated with the age in the entire population and patients with hypothyroidism (r: -0.255, $P=0.028$; $r=-0.346$, $P=0.036$ respectively). The irisin level was positively correlated with the TSH ($r=0.247$, $P=0.034$) but negatively with the fT_4 ($r=-0.316$, $P=0.006$) in the entire population. Obesity, fT_4 and irisin level were identified to be independent predictors in the diagnosis of hypothyroidism in the multivariable logistic regression analysis.
Conclusions
To the best our knowledge, this study is the first in literature to identify that obesity, irisin level and fT_4 level are independent risk factors on hypothyroidism.

DOI: 10.1530/endoabs.37.EP1022

EP1023

The relationship between oxidative stress and thyroid autoantibodies in patients with Hashimoto's thyroiditis

İhsan Ates[1], F Meriç Yılmaz[2], Mustafa Altay[3], Nisbet Yılmaz[3] & Serdar Güler[1]
[1]Department of Endocrinology and Metabolism, Ankara Numune Education and Research Hospital, Ankara, Turkey; [2]Department of Biochemistry, Ankara Numune Education and Research Hospital, Ankara, Turkey; [3]Ankara Numune Education and Research Hospital, Ankara, Turkey.

Background
The relationship between Hashimoto's thyroiditis (HT) and oxidative stress (OS) has been investigated in several studies that have included a limited number of patients, the findings have not been conclusive, which indicates that additional research that investigates parameters of OS in larger patient populations is needed. As such, this dissertation study aimed to determine the levels of parameters of OS and their relationship with thyroid antibodies in HT patients in the euthyroid, subclinical, and overt hypothyroidism stages.
Methods
This study included 93 treatment-naïve HT patients aged >18 years and 31 healthy volunteer controls with no known disease. TSH, sT_4, anti-TPO, and anti-Tg were measured via ECLIA, and serum total antioxidant status (TAS), total oxidant status (TOS), total thiol (total-SH), paraoxonase (PON), and arylesterase were measured via the colorimetric method.
Results
The TOS level and OS index (OSI) were higher in the overt hypothyroidism group than in the other group, whereas TAS, total-SH, and arylesterase levels were lower in the overt hypothyroidism group than in the other groups. Total-SH level was similar in the control and subclinical hypothyroidism groups, but was higher in the euthyroid group than in the control and subclinical hypothyroidism groups. The log (PON) and PON/HDL levels were higher in the control group than in all three patient groups. There weren't any significant differences in the log (PON) or PON/HDL levels between the three patient groups. There was a negative correlation between the anti-TPO level, and TAS, log (PON), and PON/HDL level, and between the total SH and anti-Tg levels. Overt hypothyroidism was an independent predictor of the level of all oxidative stress parameters, except for total-SH.

Conclusion
This study examined numerous parameters of OS according to HT stages. The findings provide a general picture of how OS might be affected by thyroid hormone and thyroid autoantibody levels in patients with HT.

DOI: 10.1530/endoabs.37.EP1023

EP1024

The relationship between procalcitonin and thyroid autoantibodies in patients with Hashimoto's thyroiditis

İhsan Ates, Ali Öncül, Mustafa Altay & Canan Topçuoğlu
[1]Department of Internal Medicine, Ankara Numune Education and Research Hospital, Ankara, Turkey; [2]Departmen of Biochemistry, Ankara Numune Education and Research Hospital, Ankara, Turkey.

Background
Procalcitonin (PCT) is often an increased acute phase reactant in the bacterial infection-related inflammation, and its serum level is reported elevated in several autoimmune disease. However, the level of PCT and its relationship with autoimmunity remain unknown in Hashimoto's thyroiditis (HT). Our objective was to investigate the serum levels of PCT and its association with autoantibodies in patients with euthyroid HT.
Methods
A total of 80 participants, 40 patients were newly diagnosed with euthyroid HT and 40 healthy volunteers with no known disease. Thyroid function tests and thyroid autoantibodies are analyzed in hormone laboratory with Electro-chemiluminescence immunoassay. The serum levels of PCTwere measured by ELISA kit.
Results
Hashimoto's thyroiditis patients had higher median PCT levels than those of the control group (34.3 pg/ml vs 27.8 pg/ml respectively; $P=0.037$). In the entire population and HT group, the PCT level was positively correlated with systolic and diastolic blood pressures (the entire population; r: 0.320, $P=0.004$; $r=-0.267$, $P=0.017$; HT; r: 0.355, $P=0.025$; $r=0.420$, $P=0.007$). PCT and TPO levels were identified to be an independent predictor in diagnosis of HT in the multivariate logistic regression model. An increase of one unit in the PCT level increased the risk for HT by 1.478 times and an increase of one unit in the anti-TPO level increased the risk for HT by 1.164 time when the other risk factors were kept constant.
Conclusion
Procalcitonin being the independent predictor of HT, as indicated in the multivariate regression analysis, suggests that PCT could be a hormone associated with the autoimmunity. Extensive and further researches are needed in this field.

DOI: 10.1530/endoabs.37.EP1024

EP1025

Mimic the symptoms of thyroid disorders in pregnant women

Sima Nazarpour[1], Fahimeh Ramezani Tehrani[2], Masoumeh Simbar[1], Maryam Tohidi[3], Fereidoun Azizi[3] & Hamid Alavi Majd[4]
[1]Department of Reproductive Health and Midwifery, Faculty of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [2]Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [3]Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [4]Department of Biostatistics, Faculty of Paramedicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Introduction
The prevalence of these disorders in pregnant women is relatively high and may affect mother and foetus adversely if they are not evaluated and treated appropriately. Therefore, their diagnosis and treatment is very important. On the other signs and symptoms of thyroid disease can often be masked by the physiologic changes of pregnancy and are not found. The aim of this study was to evaluate the physiological symptoms similar to thyroid disorders and their incidence in pregnant women without thyroid disorders.
Materials and Methods
This study is a population based cross sectional study. A total number of 1600 pregnant women were selected with population based cluster method in prenatal care centres. After questioning the women about the symptoms of thyroid disease and relevant clinical examination, blood samples were taken for thyroid tests and serum T_4, TSH, T3 uptake and TPOab were measured.
Result
63.5% of the participants in this study had normal thyroid function. The prevalence of overt hypothyroidism and hyperthyroidism were 3.8 and 0.8%, respectively and 29.8% of patients had subclinical hypothyroidism. 64.0% of pregnant women without thyroid dysfunction had one or more of the symptoms of thyroid disorders. 24.3% of them had one or two symptoms and 41.5% of them have three or more of the symptoms of thyroid disorders in pregnancy. Most symptoms was laziness and drowsiness (30.3%), followed by fatigue (20.3%). 2.2% of pregnant women have goitre and the symptoms were minimal.
Discussion
The correct planning in order to evaluate and diagnose thyroid disorders during pregnancy is important. Understanding the value and interpretation of thyroid function tests during normal pregnancy is necessary to discriminate between anticipated changes, pathological changes appear.

DOI: 10.1530/endoabs.37.EP1025

EP1026

An unusual clinical presentation of subacute thyroiditis in a patient with Hashimoto thyroiditis

A Serap Yalin[1], Erdem Turemen[1], Mithat Biyikli[1], Omer Aydiner[2], Ozgur Sarica[2], Saime Ramadan[3] & Kezban Berberoglu[4]
[1]Division of Endocrinology and Metabolism, Anadolu Medical Center, Istanbul, Turkey; [2]Department of Radiology, Anadolu Medical Center, Istanbul, Turkey; [3]Department of Pathology, Anadolu Medical Center, Istanbul, Turkey; [4]Department of Nuclear Medicine, Anadolu Medical Center, Istanbul, Turkey.

Hashimoto thyroiditis (HT) is the most common cause of hypothyroidism. Subacute thyroiditis (SAT) is an uncommon disease with characteristic clinical features. Co-existence of HT and SAT is very rare and diagnosis can be challenging.
Case
A 42-year-old woman with HT and multinodular goitre under levothyroxine sodium (LT_4) therapy admitted to internal medicine clinic with 1 month history of anterior neck pain radiating to jaw. Thyroid function tests (TFT), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were normal. Neck ultrasonography (NUS) revealed a hypovascular focal area in right lobe (RL) which could be consistent with thyroiditis. However, NUS showed an increase in the size of focal area a week later. She was referred to endocrinology clinic for differential diagnosis (DD). Complaints were consistent with SAT, however TFT, ESR and CRP were normal. LT_4 was stopped due to the possibility of thyrotoxicosis in SAT and to perform thyroid scintigraphy (TS). She was anxious and had another NUS by her own will 12 days later. NUS reported further progression of area in RL, and formation of a new area in left lobe (LL) with a suspect of thyroid lymphoma (TL). TS revealed decreased LL activity and increased background activity. DD included three rare situations: TL, painful HT and SAT co-existing with HT. Clinical presentation was consistent with SAT, however no inflammatory response and thyrotoxicosis developed. TL is more prevalent in HT but rarely painful. However, rapid progression of NUS findings suggested lymphoma possibility. We performed fine needle aspiration biopsy (FNAB) to exclude TL. FNAB demonstrated giant cells compatible with SAT. During 6 months of follow up thyrotoxicosis was not observed and thyroid stimulating hormone increased gradually. LT_4 was initiated again. She refused steroid therapy. HT, an autoimmune disease, can alter the course of SAT and FNAB may be required for DD.

DOI: 10.1530/endoabs.37.EP1026

EP1027

Association between thyroid specific genotypic variation and phenotypic expression of dyshormogenetic goitre and Hashimoto's thyroiditis in children and adolescents: a South Indian experience

B Ramesh, Verma B Aparna, R Vijayaraghavan, Bhargav P Ramakanth & B Rajesh
[1]Mediciti Institute of Medical sciences (MIMS), Hyderabad, India; [2]MIMS, Hyderabad, India; [3]Saveetha University, Chennai, India; [4]Endocare Hospital, Vijayawada, India; [5]MIMS, Hyderabad, India.

Background
Thyroid disorders are the commonest endocrine disorder after diabetes in most of the populations worldwide. Though, hypothyroidism is extremely common in children, there is acute scarcity of genetic studies leading to improper screening and treatment protocols in developing countries. The aim of this ambitious study was to screen for NIS, DUOX2 and TPO mutations in south Indian children and adolescent patients with dyshormogenetic goiter (DH) and Hashimoto's thyroiditis (HT) and to define the relationships between NIS, DUOX2 and TPO genotypes and clinical phenotypes.
Material and methods
Blood samples were collected from 20 patients with dyshormogenetic goiter (DH) and Hashimoto's thyroiditis (HT). Genomic DNA was extracted from peripheral blood leucocytes. PCR and direct sequencing were used to analyse for NIS, DUOX2 and TPO genes. Detailed clinical, biochemical and follow-up data were recorded in a structured proforma. Subjects with hypothyroidism were treated with thyroxine replacement. Detailed genetic analysis with 142 SNP (single nucleotide peptides) and eight sets of primers were done.
Results
The age of the cohort was 11 ± 4.5 (5–17) years. F:M ratio was 17:3. The type of hypothyroidism was overt and subclinical in 14 and six patients respectively. Family history of hypothyroidism was present in seven patients (35%). Genetic analysis shows that heterozygous NIS mutations were seen in five children with HT and in two children with DH. A homozygous mutation was picked up in a child with HT. No mutations were found in DUOX and TPO genes.
Conclusions
NIS gene mutations appears to be most prevalent mutations in HT and DH amongst South Indian children in this study. The iodine deficiency and ethnic factors may be responsible for this pattern. Further studies are needed to characterise hypothyroid phenotypes in children.

DOI: 10.1530/endoabs.37.EP1027

EP1028

Evaluation of unknown thyroid disorders in nursing home people

Ferit Kerim Kucukler, Yasin Simsek & Serdar Güler
Department of Endocrinology, Hitit University, Corum, Turkey.

Introduction
The prevalence of thyroid diseases increase with age. Mostly, they are undiagnosed. The lack of overt clinical appearance of hypo-hyperthyroidism in elder people increases the need for an attentive clinician to suspect and investigate for their presence. Thyroid dysfunctions, especially subclinics, are more frequently seen in older populations, have been linked to increased morbidity and mortality. Therefore, elderly people should evaluate in terms of thyroid functions.
Materials and methods
Hundred and ninety-two participant were enrolled in the study, 108 of them from the selected nursing home and 84 of them were living in their own home. All of the participants were evaluated in terms of thyroid functions, thyroid ultrasonography and osteoporosis.
Results
The nursing home participant (NP) group had 89.8% euthyroid, 3.7% subclinical hypothyroidism, 0.9% overt hypothyroidism, 0.9% overt hyperthyroidism and 4.6% subclinical hyperthyroidism, in household participants (HP) group's rates were 83.3, 9.5, 0.0, 0.0 and 7.1% respectively. NP group had 64.2%, HP group had 78.3% thyroid nodule. NP group's osteoporosis ratio was 34.7%, HP group's was 22.95.
Conclusions
There was no statistical difference between two groups in terms of distribution of thyroid dysfunction, thyroid nodules and osteoporosis.

DOI: 10.1530/endoabs.37.EP1028

EP1029

Thyroid switching and D727E polymorphism

Mustafa Altay[1], Murat Dağdeviren[2], Gülsüm Biten Güven[3] & Derun Taner Ertuğrul[1]
[1]Department of Endocrinology and Metabolism, Keçiören Education and Research Hospital, Ankara, Turkey; [2]Department of Internal Medicine, Keçiören Education and Research Hospital, Ankara, Turkey; [3]Department of Clinical Microbiology, Keçiören Education and Research Hospital, Ankara, Turkey.

Introduction
Graves' disease and Hashimoto's hypothyroidism are common thyroid diseases. However, occurrence of both clinical disorders one after the other in the same patient, is not common.
Case report
In this article, we presented two hypothyroid patients who developed clinical thyrotoxicosis during levothyroxine treatment. Both patients were treated with levothyroxine for a long time. Due to occurrence of clinical hyperthyroidism, levothyroxine treatments of the both patients were terminated. Although unmedicated follow-up for about 6 weeks period, recovery from thyrotoxicosis wasn't observed. Both of the patients were positive for TSH receptor antibody.
Results
They were diagnosed as Graves' disease on the basis of clinical signs, laboratory findings and imaging techniques, thus antithyroid treatment was initiated. In both cases, TSH receptor gene sequence analysis was performed, and in both of the patients D727E homozygous polymorphism was obtained.
Conclusions
In hyperthyroid cases with the history of hypothyroidism, switching between hypothyroidism and hyperthyroidism should be kept in mind and due to D727E polymorphism, and the other TSH receptor gene mutations, if it is possible genetic analysis should be performed.

DOI: 10.1530/endoabs.37.EP1029

EP1030

Relationship between thyroid function tests and all-cause mortality in patients on peritoneal dialysis: a prospective analysis

Juan J Díez[1], Sara Romero-Perez[2], María A Bajo[3], Pedro Iglesias[1], Cristina Grande[4], Gloria Del Peso[3], Rosario Madero[5], Marta Ossorio[3] & Rafael Selgas[3]
[1]Department of Endocrinology, Hospital Universitario Ramón y Cajal, Madrid, Spain; [2]Department of Nephrology, Hospital Universitario del Sureste, Madrid, Spain; [3]Department of Nephrology, Hospital Universitario La Paz, Madrid, Spain; [4]Department of Biochemistry, Hospital Universitario La Paz, Madrid, Spain; [5]Department of Biostatistics, Hospital Universitario La Paz, Madrid, Spain.

Background
Alterations in thyroid function tests results in patients on peritoneal dialysis (PD) might represent a risk factor for cardiovascular disease (CVD) and mortality.
Objective
To investigate the relationship of serum TSH, free thyroxine (FT_4), and triiodothyronine (T_3) concentrations with incident CVD and mortality in PD patients.
Methods
Prospective study including all patients attending our PD unit between 2003 and 2012 who had remained at least for 3 months in the PD program. All patients were followed until death, exit of PD program, loss of follow-up, or census date (September 2012). Survival time was estimated by the Kaplan-Meier method. Unadjusted and multivariate Cox regression models were used to assess the effects of several variables on the risk of death.
Results
From 169 subjects included in our program, 139 (81.8%) were euthyroid, 4 (2.4%) had overt hypothyroidism, and 26 (15.4%) had subclinical hypothyroidism. Patients in the first tertile of T_3 (<0.91 ng/ml) had a higher percentage of CVD events during follow-up (10.9%) than those in the second (0.91–1.10 ng/ml, 1.9%) and third tertiles of T_3 (>1.10 ng/ml, 1.9%, $P<0.05$). All-cause mortality was higher in patients in the first tertile of T_3 (20%) in comparison with patients in the second (3.8%) and third tertiles (5.6%, $P<0.05$). Kaplan-Meier analysis showed that median survival time for all-cause mortality were significantly lower in patients in the first tertile of T_3 ($P=0.013$). Unadjusted Cox regression analysis showed an increase in the risk of death in patients in this tertile (HR, 4.3; 95% CI, 1.48–12.45, $P=0.007$). In the multivariate (adjusted) analysis, this risk of death remained significant (HR, 3.14, 95% CI, 1.05–9.43, $P=0.041$).

Conclusions
Thyroid function tests alterations are associated with long-term incidence of CVD and mortality in uremic patients undergoing PD. In particular, low T_3 levels are significantly related to all-cause mortality in this population.

DOI: 10.1530/endoabs.37.EP1030

EP1031

Role of regulatory T cell and CTLA-4 gene as risk factor relapse in Graves' disease

Fatimah Eliana[1] & Pradana Suwondo[2]
[1]YARSI University, Jakarta, Indonesia; [2]University of Indonesia, Jakarta, Indonesia.

Introduction
Graves' disease (GD) management in Indonesia are generally preceded by administration of antithyroid drugs. Antithyroid drug delivery requires a long time to achieve remission, even more than 50% of patients who had remission can recur after antithyroid medication is stopped. The purpose of this study was to determine the role of CTLA-4 gene and regulatory T cells against recurrence in patients GD in Indonesia.
Methods
The study was conducted using a case-control in 144 patients GD, comparing patients who relapse and recurrence. Definition of relapse if the patient is declared remission after antithyroid treatment for at least 18 months, but relapsed after 12 months of antithyroid medication is stopped. Examination of CTLA-4 gene polymorphism of exon1 by the method of PCR RFLP, and the number of regulatory T cells was checked by flow cytometry.
Results
Research shows that patients with GD have higher risk of relapse if they have family history (P 0.01), degree two of ophtalmopathy (P 0.011) and enlargement of the thyroid gland exceeded the lateral edge of the sternocleidomastoideus muscle (P 0.044). GD patients with polymorphisms of CTLA-4 gene exon1 genotype GG and GA have higher risk of relapse than the AA genotype (P 0.003 and OR6.545). The number of regulatory T cells in patients with relapsed is lower than non-recurrence ($P<0.005$). GD patients with the G allele in the gene CTLA-4 exon1 has had lower regulatory T cells than the A allele ($P<0.005$).
Conclusion
The risk of relapse in patients with GD can be determined prior to administration of antithyroid therapy based on clinical factors, genetics and immunology.

DOI: 10.1530/endoabs.37.EP1031

EP1032

Iodine supplementation to pregnant women is scarcely available in Brazil

Danilo Villagelin[1,2], Laura Ward[2], Roberto Santos[1], Douglas Tiago[1], Giovana Azevedo[1], Sarah Zolio[1] & Joao Romaldini[1]
[1]Pontificia Universidade Católica de Campinas, Campinas, Brazil; [2]University of Campinas, Campinas, Brazil.

Introduction
A woman's iodine requirements increase substantially during pregnancy to ensure adequate supply to both mother and fetus. The deficiency of this element may cause several maternal-fetal repercussions. For this reason, iodine supplementation for pregnancy has been recommended and the World Health Organization (WHO) commends an iodine urinary concentration at a median UIC 150–249 μg/l. As in many other countries around the world, there is evidence of iodine deficiency among Brazilian pregnant women. In fact, a recent study identified UIC below 150 μg/l in 57% of the pregnant women investigated. Iodine supplements availability have not yet been evaluated in the country and our objective was identify the availability of dietary supplements for pregnant women in Brazil and verify the amount of iodine present on them, correlating it with the new global recommendations.
Methods
We used our national health electronic system (Anvisa's Bulário Eletrônico) to investigate the nutritional information of dietary supplements used by pregnant women through their package insert. Further, we contacted the pharmaceutical industries and consulted the Brazilian Dictionary of Pharmaceutical Specialties (DEF) 2012–2013.
Results
There are, currently, 23 dietary supplements for pregnant women in use. Based on daily iodine intake recommended by American Thyroid Association, European Thyroid Association and WHO (minimum of 150 μg/day), 52.2% out of these products contain no iodine; 13.0% contain insufficient amounts of iodine (1–149 μg); and only 34.8% contain the recommended quantity of this element.
Conclusion
Despite salt iodination, recent data indicate that at least half of Brazilian pregnant women present iodine insufficiency, reinforcing the need of iodine supplementation during the prenatal period. However, the present study indicates that just one third of the commercially available dietary supplements currently used by Brazilian pregnant women contain the internationally recommended daily iodine intake.

DOI: 10.1530/endoabs.37.EP1032

EP1033

Is there any effect of the treatment on MVP in patients with hypothyroidism and hyperthyroidism?

Yildiz Okuturlar[1], Aliye Soylu[2], Enver Tekin[1], Meral Mert[3], Serdal Cakmak[2], Ozlem Harmankaya[1] & Abdulbaki Kumbasar[1]
[1]Department of Internal Medicine, Bakirkoy Dr Sadi Konuk Education and Research Hospital, Istanbul, Turkey; [2]Department of Gastroenterology, Bakirkoy Dr Sadi Konuk Education and Research Hospital, Istanbul, Turkey; [3]Endocrinology and Metabolism, Bakirkoy Dr Sadi Konuk Education and Research Hospital, Istanbul, Turkey.

Introduction
In this study, we aimed to reveal the mean platelet volume (MPV) change with treatment in patients with hypothyroidism and hyperthyroidism.
Materials and methods
Two groups were retrospectively evaluated as 200 patients (21 male, 179 female) with hypothyroidism and 200 patients (26 male, 174 female) with hyperthyroidism. Before and after treatment in the outpatient follow. MPV values were compared.
Results
There is significant difference between MPV values before (8.8fL(6.1–12.1), 8.78fL (6.7–13)) and after (9.1fL (7–14), 9fL(6–12)) treatment in hypothyroidism and hyperthyroidism groups respectively and also MPV values increased in both groups after treatment ($P=0.001$).
Conclusion
The reason for the changes in MPV in our study can be explained in terms of the effect of the treatment on inflammatory period.

DOI: 10.1530/endoabs.37.EP1033

EP1034

Triiodothyronine is independently associated with metabolic syndrome in euthyroid middle-aged subjects

Hye Jeong Kim[1], Hyeong Kyu Park[1], Dong Won Byun[1], Kyoil Suh[1], Myung Hi Yoo[1], Jae Hyeon Kim[2], Yong-Ki Min[2], Sun Wook Kim[2] & Jae Hoon Chung[2]
[1]Soonchunhyang University Hospital, Soonchunhyang University College of Medicine, Seoul, Republic of Korea; [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea.

Background
Recent studies have shown associations of thyroid hormone levels with metabolic syndrome (MetS) among euthyroid individuals, though there have been some inconsistencies. We evaluated the relationships between thyroid hormones and MetS in euthyroid middle-aged subjects in a large cohort.
Methods
Retrospective analysis of 13 496 euthyroid middle-aged subjects who participated in comprehensive health examinations was performed. Subjects were grouped according to TSH, total triiodothyronine (T_3), total thyroxine (T_4), and T_3–T_4 ratio quartile categories. We estimated the odds ratios (OR) for MetS according to thyroid hormone quartiles using logistic regression models, adjusted for potential confounders.
Results
Twelve percent ($n=1664$) of the study subjects had MetS. Higher T_3 levels and T_3– T_4 ratio were associated with unfavorable metabolic profiles, such as higher BMI, systolic and diastolic BP, triglycerides, fasting glucose and HbA1c, and lower HDL cholesterol. The proportion of participants with MetS increased across the T_3 quartile categories (P for trend <0.001) and the T_3–T_4 ratio quartile categories (P for trend <0.001). The multivariate-adjusted OR (95% CI) for MetS in the highest T_3 quartile group was 1.249 (1.020–1.529) compared to the

lowest T_3 quartile group, and that in the the highest T_3–T_4 ratio quartile group was 1.458 (1.141–1.863) compared to the lowest T_3–T_4 ratio quartile group, even after adjustment for sex, age, body fat percentage, smoking, and HOMA-IR.
Conclusions
Serum T_3 levels and T_3–T_4 ratio are independently associated with MetS in euthyroid middle-aged subjects. Longitudinal studies are needed to define this association and its potential health implications.

DOI: 10.1530/endoabs.37.EP1034

EP1035

Hypothyroidism related to blocking TSH receptor antibodies after allogenic haematopoietic stem cell transplantation

Kanza Benomar[1], Catherine Massart[2], Leonardo Magro[1], Anne Sophie Parent[1], Michèle D'Herbomez[1], Ibrahim Yacoub-Agha[1], Jean Louis Wemeau[1] & Marie Christine Vantyghem[1]
[1]Department of, Endocrinology and Metabolism, Biology, Blood Diseases, Lille University Hospital, Lille, France; [2]Department of Biochimy and Hormonology, Rennes University Hoispital, Rennes, France.

Besides total body irradiation and immunosuppressive drugs, massive iodine supply and stress might participate in thyroid dysfunction, described in 50% of allo-HSCT. We report on a rare case of hypothyroidism related to blocking TRAb. A 55-year-old man was admitted for asthenia, dyspnea, myalgia, 8 kg-weight gain, constipation, dry skin, hoarse voice, recent deafness. He had moon face without any goiter. He had received, 1 year before, an unrelated 9/10 human leukocyte antigen matched allo HSCT for acute myeloid leukemia after chemotherapy including antilymphocyte serum and had achieved full female donor chimerism. He developed an acute graft-vs-host disease (GvHD) grade II 1 month post-transplantation treated with ciclosporine. Laboratory tests showed high blood cholesterol (3.53 g/l–*n*: 1.5–2.4), triglycerides (2.70 g/l–*n*: 0.3–1.50), CPK (2623U/l–$n<195$), TSH (99 mUI/ml; $n>3.5$) levels as well as antithyroperoxidase (179 U/ml; $n>5$) and TSH receptor antibodies (TBII: 102 U/l; $n<1$) levels with undetectable FT_4 and anti-thyroglobulin antibody. The functional study of TBII confirmed high blocking (TRAbs 92%; $n<30$) and low stimulating (TSAbs 58%; $n<125$) activities. The immunophenotype showed a lymphopenia with an increased CD4+(48.7%; *n*:38–46) and low CD8+(28%; *n*: 31–40) percentages. Indeed, the development of autoimmune hypothyroidism is frequent post allo-HSCT and requires regularly monitoring of TSH, given the difficulty of diagnosis in patients whose complaints can easily be attributed to the causal disease or GvHD. Immunological dysregulation during T-cell engraftment may also favour hyperthyroidism, sometimes preceded by a hypothyroid episode related to blocking TBII, called immune reconstitution syndrome. This rare and delayed syndrome has been reported in children post allo-HSCT (Sinha Thyroid 2013) or HIV (Sheikh AIDS 2014) treatment and coincided with a rapid expansion in naïve and total CD4. TSAbs and TBAbs have been shown to have similar characteristics (high affinity and similar binding epitopes on the TSH-R; morgenthaler JCEM 2007). The occurrence of 'switching' emphasizes the need for careful patient monitoring and management.

DOI: 10.1530/endoabs.37.EP1035

EP1036

Prevalence of hypothyroidism in a large series of adult thalassemic patients

Raffaella Radin[1], Leila Danesi[1], Alberto Ambrogio[1], Elena Cassinerio[2], Laura Zanaboni[2], Maria Domenica Cappellini[2], Marina Baldini[2], Maurizio Poggi[3], Chiara Ottaviani[3], Vincenzo Toscano[4], Marco Zavattaro[5], Francesco Cavagnini[6], Luca Persani[7] & Massimo Scacchi[8]
[1]IRCCS, Istituto Auxologico Italiano, Milan, Italy; [2]Cà Granda Foundation Ospedale Maggiore Policlinico, Milan, Italy; [3]II Faculty of Medicine, Sapienza University of Rome, Rome, Italy; [4]Sapienza, University of Rome, Rome, Italy; [5]Università del Piemonte Orientale 'A. Avogadro', Novara, Italy; [6]Istituto Auxologico Italiano IRCCS, Neuroendocrinology Research Laboratory, Cusano Milanino, Italy; [7]Department Medical Sciences and Community Health, IRCCS Istituto Auxologico Italiano, University of Milan, Milan, Italy; [8]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy.

Hypothyroidism has been traditionally described as a frequent endocrine complication of thalassemic children: in these patients hypothyroidism is mainly of primary origin and not linked to autoimmunity (Mariotti *et al*., Pediatr Endocrinol Rev 2011). Fewer data are available on the prevalence and nature of this complication in adult age thalassemia. Therefore, we elected to evaluate thyroid function and autoimmunity in a large series of adult patients.
Study
Ninety-five adult thalassemic subjects (48 women and 47 men, mean age 38.1 ± 6.9 years) underwent assessment of thyroid function (fT_3, fT_4 and TSH) and thyroid autoimmunity (anti-thyroid peroxidase and anti-thyroglobulin antibodies). Serum ferritin was also measured in all patients, who were regularly taking iron-chelating drugs. Hormone deficiencies other than hypothyroidism were adequately replaced.
Results
Thirty-one patients (32.6%), 16 men and 15 women, aged 39.5 ± 6.7 years, turned out to be affected by hypothyroidism. Two of them had previously undergone-thyroid surgical removal for multinodular goitre and carcinoma, respectively. The stratification by age of the other hypothyroid subjects disclosed a prevalence of 25% (2/8) among those aged 20–30, 27% (10/37) among those aged 30–40, and 36% (16/44) among those aged 40–50. No hypothyroid patients displayed anti-TPO or anti-TG antibodies. No cases of secondary hypothyroidism were observed. Mean serum ferritin was not significantly different between hypothyroid and euthyroid thalassemic subjects (1067.7 ± 664.5 vs 868.0 ± 743.5 ng/m, NS, respectively).
Comment
Hypothyroidism, primary in all cases, was highly prevalent in our series, being present in one third of the patients. This endocrine complication was equally distributed among genders and its prevalence appeared to progressively increase with age. Since measurement of serum ferritin expresses an estimation of the current degree of iron overload and not its evolution within the clinical history of patients, our data cannot rule out a contribution of secondary hemosiderosis to the pathogenesis of hypothyroidism in thalassemia.

DOI: 10.1530/endoabs.37.EP1036

EP1037

Thyroidectomy: analysis of 184 cases in a single centre

Gema López Gallardo, Francisco Javier Gómez Alfonso, Julia Silva Fernández, Álvaro García Manzanares, Inés Rosa Gómez & María López Iglesias
Mancha Centro General Hospital, Alcázar de San Juan, Spain.

Aim
To evaluate whether differences exist in terms of patient, radiological, tumour characteristics and surgical complications between malignant and benign thyroidectomy.
Materials and methods
184 correlatives cases of thyroidectomy during the period from October 2011 to October 2013 are analysed. Patient, ultrasound, tumour and complication characteristics are compared. Categorical data are reported as percentages. Characteristics between the two groups are compared using a Student's *t*-test for continuous variables and a Fisher's exact test or a χ^2 test for categorical variables.
Results
A female: male ratio of 5:1 (157 women: 28 men) is found with eight malignant cases (28.6%) in men and 35 (22.3%) in women. Malignancy is associated with family cancer history (RR: 0.3 (0.183–0.143)), and larger tumour size with benignity. Benignity nodules are 1, 21 cm larger than malignity nodules (*P*: 0.00 (0.474–1.567). No statistically significant differences in terms of age, mean operative time, mean postoperative hospital stay and surgical complications are found.
Conclusions
The nodule size is not an accurate predictor of thyroid cancer. Malignant thyroidectomy is not associated with more surgical complications or post-operative hospital stay.

DOI: 10.1530/endoabs.37.EP1037

EP1038

IL-2, IL-4, IL-5, IFN-γ and TNF-α levels in Turkish patients with Hashimoto's thyroiditis

Guzin Fidan Yaylali[1], Bedia Guleryuz[2], Fulya Akin[1], Sebahat Turgut[3], Senay Topsakal[1], Melek Tunc Ata[3] & Mukaddes Mengen Dalyanoglu[3]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Pamukkale University, Denizli, Turkey; [2]Department of Internal Medicine, Faculty of Medicine, Pamukkale University, Denizli, Turkey; [3]Department of Physiology, Faculty of Medicine, Pamukkale University, Denizli, Turkey.

Background
Hashimoto's thyroiditis (HT) is one of the most common autoimmune thyroiditis that characterised by lymphocytic infiltration and thyroid hormonal disturbances. Genetic and environmental factors play a role in etiology of the disease, but genetic factors are most common. In this study, we investigated the association between Hashimoto's thyroiditis and IL-2, IL-4, IL-5, TNF-α and IFN-γ levels.
Methods
We performed a case–control study that included 139 cases with HT (50 euthyroid, 50 subclinical hypothyroid, 39 overt hypothyroid patients) and 50 healthy control. Subjects were collected from Endocrinology Clinic of Pamukkale University in Turkey. Serum levels of glucose, insulin, PTH, Ca, phosphorus (P), alkaline phosphatase (ALP) were measured and IL-4, IL-5, TNF-α, IFN-γ analysis were performed with ELISA.
Results
IL-2, IL-4, TNF-α and IFN-γ levels were significantly higher in Hashimoto's thyroiditis patients, there were no significant differences between the groups regarding IL-5 levels. There were no significant differences detected in PTH, ALP and Ca levels.
Conclusion
Because of the HT is an inflammatory disease significantly high IL-2, IL-4, TNF-α and IFN-γ level were observed in HT. Practitioners should take into consideration IL-2, IL-4, TNF-α and IFN-γ levels in HT diagnosis. These inflammatory markers may have an important role in the pathogenic pathway in HT.
Disclosure
Grant numbers 2012 TPF6.
DOI: 10.1530/endoabs.37.EP1038

EP1039

Descriptive analysis of the histopathological findings of a series of 1567 thyroidectomies

Dulce Ma Calderón[1], Manuel Delgado[2], Enrique Castro[3], Jose Joaquín Alfaro[4], Gema López[5], José López[3] & Jaime Aranda[1]
[1]Hospital Virgen de la Luz, Cuenca, Spain; [2]Hospital General de Ciudad Real, Ciudad Real, Spain; [3]Hospital Virgen de la Salud, Toledo, Spain; [4]Hospital General de Albacete, Albacete, Spain; [5]Hospital La Mancha Centro, Alcázar de San Juan, Spain.

Introduction
We wanted to analyse the pathology results of thyroidectomies performed in the hospitals of Castilla La Mancha (Spain) between the years 2010 and 2013, inclusive.
Material and methods
A retrospective, multicentre, descriptive study of the histopathological results of the 1567 thyroidectomies performed in the hospitals of the eight health districts in our region between the years 2010 and 2013.
Results
The histopathological results were benign in 1124 cases (colloid goiter/adenomatous 42.7%, follicular adenoma 9.7%, Hurthle cell adenoma 2.7%, Graves' disease 2.6%, lymphocytic thyroiditis 7.7%, thyroiditis de Quervain 0.1%, thyroid cyst 0.4%, normal thyroid 0.4%, and other 5.6%) and malignant in 402 cases (papillary microcarcinoma 7.5%, macropapillary carcinoma 14.9%, follicular 1.5%, medullar 1.3%, anaplastic carcinoma 0.1%, parathyroid carcinoma 0.1%, and other 0.3%), and unknown in 2.6% of cases.
Conclusions
During the years 2010–2013,1567 thyroidectomies were performed in the hospitals of Castilla La Mancha. In 1124 cases (71.7%) the histopathology was benign and in 402 cases (25.6%) malignant. The most common tumour was papillary carcinoma.
DOI: 10.1530/endoabs.37.EP1039

EP1040

Sensitivity and specificity of thyroid cytology in the diagnosis of malignancy: results of a series of 1567 thyroidectomies

Dulce Ma Calderón[1], Sandra Herráiz[2], Julia Sastre[3], Abel González[4], Belén Fernández[4], Miguel Angel Valero[5] & Miguel Aguirre[4]
[1]Hospital Virgen de la Luz, Cuenca, Spain; [2]Hospital Universitario de Guadalajara, Guadalajara, Spain; [3]Hospital Virgen de la Salud, Toledo, Spain; [4]Hospital General de Ciudad Real, Ciudad Real, Spain; [5]Hospital Nuestra Sra. del Prado, Talavera de la Reina, Spain.

Introduction
Sensitivity and specificity of thyroid cytology in our series of thyroidectomies were evaluated.
Material and methods
A retrospective, multicentre study of 1567 thyroidectomies performed in the eight hospitals of Castilla La Mancha (Spain) during the years 2010–2013.
Results
The cytological results were benign in 37.6% of cases, malignant or suspicious of malignancy in 17.3% (10 and 7.3% respectively). In 4.1% of cases the cytology was atypical or indeterminate and in 12.5% follicular proliferation/follicular lesion. There were 8% non-diagnostic cytologies. In patients whose prequirúgical FNA was nondiagnostic, 20.6% had a carcinoma. Overall, 25.6% of patients had thyroid carcinoma. The sensitivity and specificity of suspicion of malignancy or malignant thyroid cytology for the diagnosis of malignancy was 75.8 and 90.3% respectively. There were 3.5% false positive and 4.5% false negative results.
Conclusions
Thyroid cytology is the diagnostic technique of choice for the study of thyroid nodule. The results in terms of sensitivity, specificity and nondiagnostic cytology in our series are acceptable.
DOI: 10.1530/endoabs.37.EP1040

EP1041

Surgical treatment of thyroid disease: descriptive analysis and histopathology of a series of 92 cases

Dulce Ma Calderón[1], Jaime Aranda[1], José Mondéjar[2], Mubarak Alramadan[1], David Martín[1] & José Pérez[1]
[1]Hospital Virgen de la Luz, Cuenca, Spain; [2]Universidad de Castilla La Mancha, Cuenca, Spain.

Introduction
Retrospective study of patients undergoing thyroid surgery at the Hospital Virgen de la Luz, Cuenca (Spain) during the years 2010–2013.
Material and methods
We evaluated data of 92 patients basically with nodular thyroid disease, who were studied and treated in our hospital.
Results
Our series is made up of 92 patients (25% men and 75% women) with an average age of 52 years. The most common form of presentation (47.8%) was recent emerging thyroid nodule, having less than a year. In 19 cases (20.6%) it was found incidentally, mainly by ultrasound. In most cases, 58 (63%), monitoring prior to surgery was $\leq$1 year. Ultrasound findings showed mostly mixed multiple nodules (32.6%). The results of cytology were nondiagnostic in 7.6%, 35.9% benign, atypical 2.2%, 9.8% follicular proliferation, suspicious of malignancy 6.5%, and 10.9% malignant. In 25 cases (27.1%) was not done FNA. In 86.9% thyroid function was normal. Total thyroidectomy was performed in 78.3%, in 20.6% hemithyroidectomy and bilateral subtotal thyroidectomy in 1.1%. Surgery was performed in 65% of cases by the most experienced surgeon. The pathology was benign in 70.6% and malignant in 29.3% cases.
Conclusions
The most common presentation in our thyroid disease amenable to surgical treatment is emerging thyroid nodule. In 20.6% of cases it was an incidental finding. Total thyroidectomy was the technique of choice (78.3%). 29.3% of the cases presented a thyroid carcinoma.
DOI: 10.1530/endoabs.37.EP1041

EP1042

Iodine nutritional status among adolescent girls in Uttarakhand State, India

Umesh Kapil
All India Institute of Medical Sciences, New Delhi, India.

Introduction
Iodine is an essential micronutrient. Iodine deficiency (ID) among adolescent girls could lead to ID amongst the newborns as they are the future mothers. Uttarakhand state is a known endemic region for ID.

Objective
The present study was conducted with an objective to assess the iodine nutritional status amongst adolescent girls in districts: Udham Singh Nagar (USN), Nainital (N), and Pauri (P) of Uttarakhand state.
Methods
In each district, 30 clusters (schools) were identified by utilising population proportionate to size (PPS) cluster sampling methodology. In each school, 60 girls (12–18 years) attending the schools were included. A total of 5430 girls from USN (1823), N (1811), and P (1796) were studied. Clinical examination of thyroid of each girl was conducted. From each cluster, on the spot urine and salt samples were collected from 20 girls.
Results
Total goitre rate (TGR) was found to be 6.8% (USN), 8.2% (N), and 5.6% (P) respectively. Median urinary iodine concentration (UIC) levels were 250 μg/l (USN), 200 μg/l (N), and 183 μg/l (P) indicating adequate iodine status amongst the study population. The percentage of families consuming salt with iodine content of <15 p.p.m. were 59.5 (USN), 44.0 (N), and 46.7 (P) percent.
Conclusion
Findings of the present study documented that adolescent girls had adequate iodine nutritional status in three districts of Uttarakhand.

DOI: 10.1530/endoabs.37.EP1042

EP1043

Ultrasonographical features and cytological findings of thyroid nodules in patients with Hashimoto's thyroiditis

Didem Ozdemir[1], Fatma Dilek Dellal[2], Husniye Baser[2], Aylin Kilic Yazgan[3], Seyda Turkolmez[4], Reyhan Ersoy[1] & Bekir Cakir[1]
[1]Department of Endocrinology and Metabolism, School of Medicine, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey; [2]Department of Endocrinology and Metabolism, Ataturk Education and Research Hospital, Ankara, Turkey; [3]Department of Pathology, Ataturk Education and Research Hospital, Ankara, Turkey; [4]Department of Nuclear Medicine, School of Medicine, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey.

Introduction
It is unclear whether ultrasonographic (US) findings and fine-needle aspiration biopsy (FNAB) results of nodules accompanied with Hashimoto's thyroiditis (HT) are affected by the presence of thyroiditis or not. In this study, we compared US features and cytological results of nodules in patients with and without HT.
Methods
Patients who underwent FNAB in our clinic were evaluated prospectively. Nodules in patients with and without HT were categorised as groups 1 and 2 respectively. Cytological results were classified as benign, atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasia suspicion, malignancy suspicion, malignant, and nondiagnostic.
Results
181(35.5%) patients with HT and 329 (64.9%) without HT were included in the study. There were totally 800 nodules, 288 (36%) in group 1 and 512 (64%) in group 2. Ultrasonographically, presence of hypoechoic halo and marginal irregularity were similar in two groups ($P=0.12$ and $P=0.20$ respectively). Microcalcification was present in 11.8% of nodules in group 1 and 20.3% in group 2 ($P=0.002$). Macrocalcification was detected in 19.5 and 23.8% of nodules in groups 1 and 2 respectively ($P=0.01$). 30.6% of nodules in group 1 was hypoechoic, 66.3% was isoechoic, and 3.1% was hyperechoic. In group 2, 40.2% was hypoechoic, 58.4% was isoechoic, and 1.4% was hyperechoic ($P=0.01$). Solid texture was observed in 78.1% of nodules in group 1 and 62.3% of nodules in group 2 ($P<0.001$). Cytological results were as follows; in group 1, 78.1% benign, 2.4% AUS/FLUS, 0.3% malignancy suspicion, 1.7% malignant, and 14.6% nondiagnostic; in group 2, 81.4% benign, 2.3% AUS/FLUS, 0.4% follicular neoplasia suspicion, 1.0% malignancy suspicion, 1.4% malignant, and 13.5% nondiagnostic ($P=0.78$).
Conclusion
Suspicious US features such as microcalcification, macrocalcification and hypoechoic appearance are found with a lower prevalence in nodules accompanying HT. Cytological results were similar in patients with and without HT.

DOI: 10.1530/endoabs.37.EP1043

EP1044

Usefulness of the assessment of thyroid blood flow as a predictor of relapse of Graves' disease

Agustín Angel Merchante[1], Lourdes García-Blasco[2], Susana Pérez[1], Amparo Fabra[2], Pilar Cubells[1] & Carlos Sánchez[2]
[1]University General Hospital of Castellón, Castellón de la Plana, Spain; [2]University General Hospital of Valencia, Valencia, Spain.

Objective
We investigated the clinical usefulness of thyroid blood flow measurement by colour-flow Doppler ultrasonography in predicting relapse of Graves' disease (GD).
Patients and methods
In 30 euthyroid GD patients, (eight males and 23 females), aged 17–68 years (mean 43.8 ± 12.8), after at least 1 year of treatment with anti-thyroid drug (ATD) and just before its withdrawal, we evaluate with colour-flow Doppler ultrasonography the colour-flow Doppler mapping (the amount of flow was classified on four point scale, 0–3) and we calculate, in pulsed Doppler mode, the peak systolic velocity in the inferior thyroid artery (ITA–PSV). All ultrasound examinations were performed by the same endocrinologist expert in thyroid ultrasound using a duplex Doppler apparatus (Logic Scan 64, B-Side Medical System) with an 8 MHz linear array probe. Clinical data was collected and measurements of TSH, serum free thyroxine, and TSH receptor antibodies were performed. GD relapse was defined as an increase in the serum level of FT_4 to above the normal upper range and suppression of serum TSH in 18 months after removal of ATD. Mann–Whitney *U* test and Fisher's exact test were used for statistical analysis. The sensitivity and specificity were calculated using a 2×2 table.
Results
In relapse group ($n=14$, 47%) ITA–PSV was significantly higher than in the non-relapse group ($n=16$), (48.5 ± 17.7 cm/s vs 32.6 ± 9.5 cm/s, $P=0.01$). For prediction of GD relapse, the best cut-off value was 35 cm/s for ITA–PSV. Sensitivity was 71%, specificity 87%, positive predictive value 83%, and negative predictive value 78%. All patients with grade 3 in colour-flow Doppler mapping ($n=3$) had an early relapse of GD (before the first 6 months).
Conclusions
Colour-flow Doppler mapping study and measurement of ITA/PSV in euthyroid GD patients immediately before withdrawal of ATD may assist in the prediction of GD relapse.

DOI: 10.1530/endoabs.37.EP1044

EP1045

The effect of anti-TNF therapy on thyroid function in patients with inflammatory bowel disease

Stavroula A Paschou[1], Fotios Kothonas[2], Alexandros Myroforidis[2], Vasiliki Loi[1], Olympia Karayianni[1], Androniki Poulou[2], Konstantinos Goumas[2] & Andromachi Vryonidou[1]
[1]Department of Endocrinology and Diabetes, Hellenic Red Cross Hospital, Athens, Greece; [2]Department of Gastroenterology, Athens, Greece.

Introduction
Inflammatory bowel disease (IBD) has been associated with various disorders of thyroid function. Many of these patients are now treated with biological agents targeting on TNF-a.
Aim
To investigate thyroid function in patients with IBD and the potential effect of anti-TNF therapy.
Patients and methods
We studied 41 patients with IBD (25M/16F, 36.4 ± 11 years), without any known thyroid disorder. Eighteen patients (9M/9F, 33.6 ± 8.8 years) were on anti-TNF therapy for more than 1 year, while 23 patients (16M/7F, 38.7 ± 12.5 years) were treated with azathioprine and mesalazine (Aza/Mes). Nine patients from the second group were then treated with anti-TNF and studied again 6 months later. We assessed thyroid function by measuring T_3, FT_4, TSH, anti-TG, and anti-TPO levels.
Results
One patient presented with clinical and one with subclinical hyperthyroidism. Thyroid auto-antibodies were positive in 12.2% (one anti-TG and four anti-TPO). Patients from the anti-TNF group had reduced levels of FT_4 (1.09 ± 0.15 ng/dl vs 1.38 ± 0.9 ng/dl, $P=0.042$), with no differences in T_3 levels (1.8 ± 0.28 nmol/l vs 2.02 ± 1.7 nmol/l) and TSH (1.76 ± 0.8 mIU/ml vs 1.58 ± 0.9 mIU/ml, $P>0.05$). The percentage of patients with positive thyroid auto-antibodies were lower in the

anti-TNF group, 5.6% (1/18) vs 17.4% (4/23), but without statistical significance ($P>0.05$). In patients who were treated for 6 months with anti-TNF, we found statistically significant reduction in FT_4 (1.24 ± 0.26 ng/dl vs 1.11 ± 0.16 ng/dl, $P=0.048$), without changes in T_3 (1.5 ± 0.43 nmol/l vs 1.8 ± 0.2 nmol/l) and TSH (1.82 ± 1.28 mIU/ml vs 1.68 ± 0.96 mIU/ml), in all comparisons $P>0.05$. There was no change regarding thyroid auto-antibodies.
Conclusions
Patients with IBD showed high percentage of thyroid autoimmunity, while the functional thyroid disorders presented were clinical and subclinical hyperthyroidism. Treatment with anti-TNF resulted in reduced levels of FT_4, without changes in T_3, TSH, and thyroid auto-antibodies.

DOI: 10.1530/endoabs.37.EP1045

EP1046

Hypo- and hyperthyroidism: causes of hepatic dysfunctions

Lencu Codruta[1], Iacob Adrian[1], Lencu Monica[2] & Georgescu Carmen[1]
[1]Department of Endocrinology, 'Iuliu Hatieganu' University of Medicine and Pharmacy, Cluj-Napoca, Romania; [2]4th Medical Clinic, 'Iuliu Hatieganu' University of Medicine and Pharmacy, Cluj-Napoca, Romania.

Background and aims
The aim of this study is to analyse the serum markers of liver function and the morphological hepatic changes (by ultrasound) in hypo- and hyperthyroidism.
Methods
The study included 59 patients with hypothyroidism: subclinical disease 14 patients and clinically manifest disease 45 patients, and 30 patients with hyperthyroidism. All patients underwent serum liver function tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (Bt), gamma-glutamyl transpeptidase (GGTP), alkaline phosphatase (SAP), and ultrasound monitoring of the liver. The results were compared to those of a control group of 30 patients with the same age and sex parameters.
Results
In hypothyroidism, increased ALT levels were found in 35.60% of the patients, and nonalcoholic fatty liver disease (NAFLD) was present in 37.30% of the patients; there was an inversely proportional linear correlation with a high statistical significance between free T_4 vs ALT, free T_4 vs AST and a directly proportional correlation between TSH vs ALT, TSH vs AST, and TSH vs GGTP. In hyperthyroidism, the prevalence of liver test changes in the patients was as follows: ALT and AST 23.3%, Bt 36.6%, GGTP 36.6%, SAP 53.3%; NAFLD 33.3%; the linear regression model evidenced a directly proportional correlation between free T_4 and the liver parameters, with a significance for Bt, SAP, and GGTP.
Conclusions
It is recommended to monitor the liver function of all patients with thyroid dysfunctions at the time of diagnosis (pre-therapy) and during the evolution of the disease under therapy.

DOI: 10.1530/endoabs.37.EP1046

EP1047

TPOAb as an autoimmune response or index of thyroid hypofunction in breast cancer?

Peter Smyth[1,2], E W M McDermott[1] & N J O'Higgins[1]
[1]UCD, Dublin, Ireland; [2]NUI (G), Galway, Ireland.

The observed association between thyroid disorders and breast cancer has provoked many investigations. One area where there is some, although far from universal, agreement is the finding of an increased prevalence of anti-thyroid autoantibodies in breast cancer patients compared to controls. Whether this is a feature of a generalised autoimmune response to breast cancer, or provoked by the enzyme thyroid peroxidase acting as an autoantigen, remains unclear. In this study we looked at thyroid antibodies in terms both of their positivity, either detectability or elevation, and their relationship to serum TSH in patients with breast cancer ($n=907$) compared to 179 postmenopausal controls. TPOAb detectability was defined as >2.0 and <20.0 kIU/l; and positivity >20.0 kIU/l. TPOAb was undetectable (≤ 2.0 kIU/l in 82.1% of controls compared to 51.8% of breast cancers; $P<0.001$). Detectable TPOAb values were (controls 3.9%; breast cancer 24.5%; $P<0.001$); elevated values (controls 14.0%; BrCa 22.9%; $P<0.01$). In the case of elevated TPOAb serum TSH was >4.0 mU/l in 61.5% of BrCa compared to 20.0% of controls. Interestingly, both TPOAb positivity and detectability were increased in BrCa patients (33.1 and 24.0%), even when TSH was within the upper 50% of the reference range (2.1–4.0 mU/l). Comparable values for controls were 11.0 and 4.8% respectively ($P<0.001$ in both cases). Thus a tendency towards higher TSH applied to patients with BrCa who had either detectable or elevated TPOAb. This finding suggests that even the marginally detectable TPOAb levels described in this study may represent more than so called 'assay noise'. They indicate, on the basis of serum TSH distribution, that TPOAb positivity may be associated with a subtle thyroid dysfunction which we and others have suggested may be beneficial in terms of breast cancer outcome.

DOI: 10.1530/endoabs.37.EP1047

EP1048

Menstrual disturbances in thyroid dysfunction

Gökçen Güngör[1], Zeliha Hekimsoy[2], Derya Öz[2], Pinar Alarslan[2], Ogün Hatiboglu[2] & Bilgin Özmen[2]
[1]Department of Internal Medicine, Medical Faculty, Celal Bayar University, Manisa, Turkey; [2]Division of Endocrinology and Metabolism, Department of Internal Medicine, Medical Faculty, Celal Bayar University Manisa, Turkey.

Introduction
Thyroid hormones play an important role in achieving and maintaining reproductive functions. Thyroid dysfunction affects the menstrual cycle and often leads to menstrual irregularity. We prospectively investigated untreated female patients presenting to our Endocrinology and Internal Medicine outpatient clinics.
Material and methods
All the patients were of reproductive age and were newly diagnosed with thyroid dysfunction. After a detailed history (including menstrual history) was taken, TSH, fT_3, fT_4, anti-Tg, and anti-TPO levels were measured and thyroid ultrasound was performed in all. Thyroid functional status was determined by measurement of TSH, fT_3, and fT_4. Patients were subdivided into the following groups: overt hypothyroidism (54 patients), subclinical hypothyroidism (106 patients), overt hyperthyroidism (50 patients), subclinical hyperthyroidism (55 patients), and euthyroid patients (Hashimoto's thyroiditis/nodular goiter, 220 patients). Women with normal routine laboratory and imaging studies were classified as controls. Thus, 485 patients and 108 healthy controls were evaluated.
Results
Among patients with overt hypothyroidism, the most frequent menstrual disorders were hypermenorrhea, menorrhagia, oligomenorrhea, and polymenorrhea. Hypermenorrhoea was significantly more common (33.3%) than in controls (5.6%) ($P<0.05$). Among hypothyroid patients, hypermenorrhoea was more common (35%) in those with severe hypothyroidism (TSH >50 μIU/ml) than in those (16.5%) with mild hypothyroidism (TSH 5–10 μIU/ml) ($P<0.05$). The prevalence of menstrual disturbances in the other groups of thyroid dysfunction patients was not significantly different than that of controls.
Conclusion
Thyroid function influences the menstrual cycle and affects reproductive activity, fertility, and pregnancy outcomes. For these reasons, investigation of thyroid function in women with abnormal menstrual activity should be performed.

DOI: 10.1530/endoabs.37.EP1048

EP1049

Brain, mood and cognition during treatment initiation in mild hypothyroidism

Eva Maria Quinque[1], Stefan Karger[2], Katrin Arélin[1,3], Matthias L Schroeter[1,4], Jürgen Kratzsch[5] & Arno Villringer[1,4]
[1]Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany; [2]Clinic for Endocrinology and Nephrology, University Hospital, Leipzig, Germany; [3]Leipzig Research Center for Civilization diseases, University of Leipzig, Leipzig, Germany; [4]Clinic for Cognitive Neurology, University Hospital Leipzig, Leipzig, Germany; [5]Institute for Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, University Hospital Leipzig, Leipzig, Germany.

In the present study, we investigated neural alterations in newly diagnosed patients with mild hypothyroidism due to Hashimoto's thyroiditis alongside mood and cognition as well as changes with treatment initiation. Animal studies and first studies of human brain metabolism using radioactive tracers suggest neural involvement in affective and cognitive symptoms of hypothyroidism. Here, we introduce non-invasive magnetic resonance imaging (MRI) techniques that allow the analysis of both brain structure and functional connectivity between brain regions and may thus help identifying neural correlates of hypothyroid symptoms. Nine patients and nine healthy matched control subjects (mean age 42 ± 5 vs 38 ± 8 years; one male each) underwent structural and resting-state functional 3T MRI scanning and comprehensive neuropsychological testing before and 3 months after treatment initiation. Voxel-based-morphometry was used to investigate grey matter density and resting-state functional MRI to analyse the connectivity of brain regions known to be involved in hypothyroidism such as the hippocampus, the amygdala and the anterior cingulate cortex. Treatment restored thyroid hormone levels to the reference range, though the overall effect was small (mean $\pm$ s.d. TSH (mU/l): pre 6.1 ± 1.2; post 3.4 ± 1.2). Patients reported significantly higher symptom load, reduced well-being and mental health compared to the control group before but not after treatment initiation. We did not find cognitive impairment or neural alterations even before treatment and no change with treatment. The observed mood alterations could not be related to brain structure or function. The attempt to relate initial treatment effects in mild hypothyroidism to changes in brain structure and function did not produce positive results. Given the small sample size and the mildness of the hypothyroidism, we cannot exclude a false negative finding regarding cognition and brain data. We still want to share the data to avoid publication bias and have thus made them available here for use in meta-analyses: http://neurovault.org/collections/169/.

DOI: 10.1530/endoabs.37.EP1049

EP1050

Thyroid function in healthy pregnant women in iodine excessive area

Yoon Young Cho, Dong Ik Cha, Jae Hyeon Kim, Jae Hoon Chung & Sun Wook Kim
Samsung Medical Center, Seoul, Republic of Korea.

Background/aims
Maternal subclinical hypothyroidism has been reported to be associated with risks of adverse pregnancy outcomes such as fetal loss and possible fetal neurodevelopmental deficit. However, current guidelines seem to overestimate subclinical hypothyroidism in pregnant women in some regions. Therefore, we aim to evaluate trimester-specific reference range of serum TSH for pregnant women in Korea and whether maternal subclinical hypothyroidism affects perinatal outcomes.
Methods
This is a prospective, observational study conducted in Samsung Medical Center between April 2012 and September 2013. Total 348 pregnant women who visited obstetrics for antenatal check-up were enrolled. Women with previous thyroid diseases or medications, positive for autoantibodies, multifetal gestation were excluded.
Results
Mean values of serum TSH in the first, second and third trimester were 1.22, 1.65 and 1.69 mIU/l respectively. Reference intervals (2.5%, 97.5%) of serum TSH in each trimesters as follows; 0.04–4.07, 0.09–4.85 and 0.32–6.07 mIU/l, respectively. According to current guidelines, 25.5% of subjects in the first trimester were diagnosed as subclinical hypothyroidism, 12.9% in the second trimester and 12.3% in the third trimester, respectively. Additionally, perinatal outcomes of these women were not different with that of subjects with normal TSH value.
Conclusions
Upper limit of reference value of serum TSH is much higher in Korean pregnant women than that of current guidelines and needs to be modified. Perinatal outcomes are favorable in pregnant women with subclinical hypothyroidism and further studies are needed to clarify long-term neurodevelopmental outcomes of offspring.

DOI: 10.1530/endoabs.37.EP1050

EP1051

Seaweed derived gaseous iodine: a source of iodine intake in coastal communities?

Peter Smyth[1,2], Robert Burns[2], Michael Casey[1], Maria Andersson[4], Karen Mullan[3] & Colin O'Dowd[1]
[1]NUI(G), Galway, Ireland; [2]UCD, Dublin, Ireland; [3]QUB, Belfast, UK; [4]ETH, Zurich, Switzerland.

This communication tests the hypothesis that iodine (I2) gas or iodine oxides released from seaweeds previously shown to enhance atmospheric iodine adjacent to seaweed hotspots, may through being inspired by respiration, supply a significant fraction of daily iodine requirements. This could assume importance in a country such as Ireland where iodised salt availability is $<5\%$. Iodine intake was assessed by measuring urinary iodine (UI) excretion using a dry ashing technique with Sandell Kolthoff colorimetry. Urine samples were obtained from schoolchildren ($n=167$) and adult ($n=481$) populations living in coastal areas, including those residing beside a seaweed hot spot, and inland areas of Ireland. Despite dietary iodine intake not varying significantly between inland and coastal communities, the median UI values in the inland areas was 72.5 μg/l (range 58–102 μg/l); coastal areas with limited seaweed growth 70.8 μg/l; seaweed hot spot 145 μg/l. The % of individual readings suggestive of iodine deficiency (<50 μg/l) were greatest in inland areas 27.9 vs 14.3% in limited seaweed growth areas. The lowest proportion of UI values <50 μg/l (3.6%) was observed in the population living beside the seaweed hot spot. Not surprisingly, the greatest number of UI values >150 μg/l (45.6%) was observed in the seaweed hot spot region. In contrast, relatively few higher UI values (>150 μg/l) occurred in the other regions (range 3.6–11.6%). It is postulated that the most infrequent evidence of iodine deficiency recorded near seaweed hotspots may be the result of atmospheric iodine compensation for inadequate dietary iodine intake through respiration in coastal areas and may assist in maintaining normal thyroid function even when dietary intake is apparently deficient.

DOI: 10.1530/endoabs.37.EP1051

EP1052

Percutaneous ethanol injection as a first line treatment of cystic thyroid nodules: experience after its introduction in a university hospital

Jordi L Reverter, Nuria Alonso, Isabel Ordoñez, Maribel Cuadrado, Lucia Cano, Dídac Mauricio & Manel Puig Domingo
Endocrinology and Nutrition Department. Germans Trias i Pujol University Hospital, Badalona, Spain.

Objectives
To evaluate the efficacy, safety and patient's pain perception of percutaneous ethanol injection treatment (PEIT) as an alternative to surgery in symptomatic thyroid cysts.
Patients and methods
Thirty consecutive patients (mean age: 46 ± 10 years; 82% women) with symptomatic thyroid cysts relapsed after drainage were included. In all cases, cytology prior to treatment, maximum cyst diameter and volume were determined. PEIT was conducted using the established procedure, and the volume of fluid removed and pain perceived by the patient were assessed. In each procedure, the volume of alcohol instilled was <2 ml. After follow-up, final cyst diameter and volume were determined and the persistence of symptoms was assessed by questionnaire.
Results
Mean symptom duration was 10 ± 20 months. All the cases had a benign cytology. A single session of PEIT was required to complete the procedure in 45% of patients two in 31% and three in 13%. Mean initial maximum cyst diameter was 3.5 ± 1.0 cm and mean extracted liquid volume 61 ± 36 ml. During PEIT, 39% of patients experienced virtually no pain, 43% mild pain and 17% moderate pain. No complications of PEIT were observed. After 9 ± 3 months follow-up, cysts were reduced more than 70% in volume in 86.3% of patients, more than 80% in 61.9% and more than 90% in 42%. Final mean maximum cysts diameter was 1.3 ± 0.6 cm. With respect to cosmetic complaints or local symptoms of compression, PEIT-treated patients presented an initial score of 22 ± 8 and 13 ± 5 after treatment ($P<0.05$) and 47% of cases reported a score of 10 (absence of symptoms).
Conclusions
In our experience, percutaneous ethanol injection has prove to be an effective, safe and well-tolerated first-line treatment of symptomatic thyroid cysts.

DOI: 10.1530/endoabs.37.EP1052

EP1053

Soft gel capsule vs liquid thyroxine formulation at breakfast: the results of 'TITI' study

Ilenia Pirola, Anna Maria Formenti, Alessandra Cristiano, Linda Daffini, Elena Gandossi & Carlo Cappelli
Department of Clinical and Experimental Sciences, Endocrine and Metabolic Unit, Clinica Medica, University of Brescia., Brescia, Italy.

Levothyroxine (l-T_4) is the mainstay of treating hypothyroidism. Despite the 'classic' tablet formulation of l-T_4, pharmaceutical industries have recently introduced other formulations such as liquid and a soft gel capsule in a few countries. Recent studies have shown a better absorption of these formulations compared with the traditional tablet bypassing the pH-depending dissolution phase and less suffering the binding by sequestrants in the intestinal lumen. Our preliminary data of the 'TICO' study, a double-blind, placebo-controlled trial aimed to evaluate the efficacy of oral liquid l-T_4 assumed at breakfast, seems to demonstrate that oral liquid thyroxine makes no difference to the thyroid hormonal profile (TSH, fT_4 and fT_3) regardless assumed before or during breakfast. Based on these preliminary data, we have conducted the 'TITI' (Tirosint® vs Tiche®, Ibsa farmaceutici Italia) study in order to verify the thyroid hormonal profile of patients assuming l-T_4 in soft gel capsule during breakfast. We have enrolled 30 (25/5 female/male, 47.1 ± 11.9 years old) euthyroid patients on stable liquid l-T_4 therapy assumed during breakfast. According to the study design all patients switched the liquid formulation to soft gel capsule maintaining the same dosage and the usual breakfast. After 6 weeks TSH, fT_4 and fT_3 values were re-tested. At the end of the study no differences to TSH serum (2.61 ± 1.44 vs 2.23 ± 1.16 mIU/l, $P = 0.269$), fT_4 (10.43 ± 1.25 vs 9.91 ± 1.26 pg/ml, $P = 0.120$) and fT_3 (2.71 ± 0.39 vs 2.88 ± 0.31 pg/ml, $P = 0.068$) were observed among the patients whether assuming liquid or soft gel capsule at breakfast. In conclusion, we have clearly demonstrated that l-T_4 soft gel capsule can be taken at breakfast without difference from liquid formulation, facilitating compliance to l-T_4 replacement therapy.

DOI: 10.1530/endoabs.37.EP1053

EP1054

The association between sick euthyroid syndrome and hs-CRP in obese patients without comorbidities

Şakir Özgür Keşkek[1], Tayyibe Saler[1], Sinan Kırım[1], Özlem Kurşun[1], Süleyman Ahbab[2], Mehmet Bankir[1] & Ömer Arif Pamuk[1]
[1]Internal Medicine Clinic, Adana Numune Training And Research Hospital, Adana, Turkey; [2]Internal Medicine Clinic, Haseki Training And Research Hospital, Istanbul, Turkey.

Inflammation has been shown in obese patients in previous studies. Sick euthyroid syndrome is an expected condition in case of inflammatory diseases. In this study, we aimed to investigate the frequency of sick euthyroid syndrome in obese patients without comorbidities and evaluate the association between obesity and inflammation. A total of 390 subjects were enrolled in this case-control study. The study group consisted of 200 obese patients without comorbidities and the control group consisted of 190 healthy subjects. Thyroid function tests, fasting glucose, insulin, serum lipids, complete blood count, erythrocyte sedimentation rate and hs-CRP levels of all patients were measured. Blood pressures, waist circumference, body mass index were reported. Groups were compared according to the hs-CRP levels and the frequency of sick euthyroid syndrome. The association between hs-CRP and sick euthyroid syndrome was evaluated. The groups were matched in terms of age and sex ($P = 0.082$, 0.186 respectively). There was statistically significant difference between the groups according to the frequency of sick euthyroid syndrome ($P < 0.001$). There was a correlation between the levels of FT_3 and hs-CRP in obese patients with sick euthyroid syndrome ($P = 0.006$). In this study, we have found an association between sick euthyroid syndrome and obesity. Moreover, we have found a correlation between sick euthyroid syndrome and hs-CRP level. These results showed that obesity (without any comorbidities) is an inflammatory disease and has systemic effects which lead to sick euthyroid syndrome ($P = 0.006$). In this study, we have found an association between sick euthyroid syndrome and obesity. Moreover, we have found a correlation between sick euthyroid syndrome and hs-CRP level. These results showed that obesity (without any comorbidities) is an inflammatory disease and has systemic effects which lead to sick euthyroid syndrome.

DOI: 10.1530/endoabs.37.EP1054

EP1055

Efficacy and safety of radiofrequency ablation performed by an endocrinologist for large benign thyroid nodules

Tae Hyun Kim, Seok Ho Seo & Soonho Kim
Kwangju Christian Hospital, Gwang ju, Republic of Korea.

Background
Radiofrequency ablation has recently been used for the treatment of benign thyroid nodules, with outstanding results. However, in most related studies, smaller nodules (< 2 cm) were included and the procedure was usually performed by a radiologist or surgeon. Therefore, this study evaluated the efficacy and safety of radiofrequency ablation for nodules > 2 cm performed by an endocrinologist with several years of experience performing fine-needle aspiration cytology.
Methods
This study was a cross-sectional analysis of 111 patients who received radiofrequency ablation between April 2010 and July 2013; 73 patients with 75 nodules > 2 cm in diameter with at least 6 months of follow-up examinations were included.
Results
The mean follow-up period was 11.5 months. The mean nodule volume decreased from 17.0 ± 15. ml preoperatively to 6.0 ± 8.5 ml postoperatively, with a mean volume reduction of 69.7%. There were no major complications, and only one patient (1.3%) presented with a minor complication (haemorrhaging of the thyroid parenchyma).
Conclusions
Radiofrequency ablation is a safe method for reducing the size of large benign thyroid nodules and is not associated with any major complications.

DOI: 10.1530/endoabs.37.EP1055

EP1056

Prediction of the size of benign thyroid nodules and an analysis of associated factors

Seok Ho Seo, Tae Hyun Kim & Soonho Kim
Kwangju Christian Hospital, Gwang Ju, Republic of Korea.

Background
Most thyroid nodules are benign therefore, they are commonly only monitored. Only a few studies are available on the natural progression/regression of benign thyroid nodules, and large-scale studies on the subject are non-existent. So we identify factors that affect the size of benign thyroid nodules and to predict the potential nodule size through a model.
Methods
Between January 2001 and December 2011, 2,469 benign thyroid nodules (1,564 patients) were diagnosed through fine needle aspiration. After excluding 505 nodules for which either the volume was unknown or percutaneous ethanol injection or radiofrequency ablation had been performed, 1,964 benign thyroid nodules (1,261 patients) were selected for the retrospective analysis in our study.
Results
The nodules with increased size overtime involved a longer follow-up period than the nodules with decreased size. The proportions of females and cystic portion were relatively high. For the thyroid nodules with increased size, we analysed the potential influencing factors. Our analysis results indicate that larger nodule volume, extended follow-up period, and high cystic proportion were all positively associated with increased nodule size.
Conclusion
Controlling for all other potential variables, the thyroid nodules tended to grow at a rate of approximately 0.034 cm^3 per year in the group with continually growing nodules. The model used in our study may offer helpful insight in determining an optimal treatment schedule for benign thyroid nodules.

DOI: 10.1530/endoabs.37.EP1056

EP1057

Investigation of GLP-1 and GIP levels change in patients with hyperthyroidism before and after treatment

Duygu Kalkan Cira, Sabahat Ozdem & Ramazan Sari
School of Medicine, Akdeniz University, Antalya, Turkey.

The main hormones responsible for the incretin effect are GIP and GLP-1. Thyroid hormones accelerate the absorption of glucose from the intestine, increase the release of glucose from glycogen stores and affect the hepatic

demolition of insulin. We aimed to assess incretin levels in patients with hyperthyroidism before and after thyroxine therapy. Total 24 subjects (12 hyperthyroid and 12 controls) were enrolled in the study. Oral glucose tolerance test was performed in patients with 75 g glucose. Glucose, insulin, C-peptide, GLP-1 and GIP levels were measured at 0, 30, 60, 90, and 120th minutes. Tests were repeated after providing euthyroidism in patients with hyperthyroidism. Basal glucose level was higher in hyperthyroidism group when compared control group ($P=0.03$). There was no statistically significant difference between groups in terms of temporal GLP-1 and GIP response for oral glucose load. Peak GLP-1 level was reached at 60 minutes and GIP was at 90 min in both groups. GLP-1 and GIP measurements did not change before and after the treatment in the hyperthyroidism group. Peak GLP-1 level was reached at 60th minutes in hyperthyroidism group before the treatment but it was reached at 30th minutes after providing euthyroidism. Peak GIP-1 level was reached at 90th minutes in hyperthyroidism group before the treatment but it was reached at 60th minutes after providing euthyroidism. These findings suggest that total incretin response for oral glucose load in patients with hyperthyroidism might be preserved. However, peak incretin responses are changed after providing euthyroidism.

DOI: 10.1530/endoabs.37.EP1057

EP1058

Liquid vs tablet levo-thyroxine formulation in de novo treatment of hypothyroidism in patients with Hashimoto's thyroiditis: tolerability and changes in quality of life

Marilena Sidoti[1] & Massimo Giusti[1,2]
[1]Centro Diagnostico Priamar, Savona, Italy; [2]Dipartimento di Medicina Interna, Università di Genova, Genoa, Italy.

Several levo-thyroxine (L-T_4) formulations are now available. However, scientific societies discourage the use of generic L-T_4 owing to its uncertain bioavailability in comparison with brand L-T_4. Recent literature data suggest that using a liquid formulation of brand L-T_4 improves the management of hypothyroidism. However, it is not clear whether patient satisfaction improves on liquid (LI) L-T_4, as patients may initially be reluctant to switch from their tablet (TA) formulation to a 'new' (LI) L-T_4. The aim of this study was to evaluate efficacy, tolerability and quality of life (QoL) changes in Hashimoto's thyroiditis patients who began de novo L-T_4 treatment for sub-clinical or overt hypothyroidism. Patients were randomized to LI ($n=15$) or TA ($n=16$) L-T_4 formulation (IBSA Farmaceutici). After 6 months, they switched from one formulation to the other. Clinical and hormonal data were collected at the baseline and after 1 (1st titration), 6 (crossover), 7 (2nd titration) and 12 (end of study) months. Hypothyroid symptoms were scored on the Billewiciz scale (BS); subjective satisfaction and QoL were evaluated by means of a visual analogic scale (VAS) and the ThyPRO inventory. On randomization, sex distribution (85% females), median age (59 years), thyroid volume (8 ml), blood pressure (systolic 120 mmHg; diastolic 80 mmHg) heart rate (70 bpm) and concomitant therapies (1 drug on average), but not BMI (TA 26.7 ± 1.3 kg/m^2, LI 22.7 ± 0.8 kg/m^2; $P=0.02$), were similar between groups. BS scores (LI 3.8 ± 0.4; TA 2.7 ± 0.4; $P=0.06$), fT_3, fT_4 (LI 7.7 ± 0.7 pg/ml; TA 9.1 ± 0.6; $P=0.1$) and TSH (LI 21.5 ± 8.4 mIU/l; TA 11.0 ± 2.5 mIU/l) were not statistically different. ThyPRO scores did not differ between groups at the baseline. In both groups, L-T_4 treatment was begun at a dosage of 50 μg/day. Before the 1st titration, sevne women (LI 27% TA 19%) withdrew their consent and dropped out. After titration, the dosages were similar in both groups (LI 46.1 ± 4.1 μg per day, TA 55.8 ± 3.0 μg per day). On crossover, clinical data remained unchanged between groups and BMI was still significantly lower ($P=0.003$) in LI (23.6 ± 0.9 kg/m^2) than in TA (26.0 ± 1.2 kg/m^2) subjects. On L-T_4 treatment, BS scores decreased in both groups (LI 2.4 ± 0.4, TA 1.3 ± 0.4; $P=0.1$). No differences were noted between groups in terms of VAS (LI 8.4 ± 0.4, TA 8.1 ± 0.4) or laboratory data. A reduction on all ThyPRO scales was noted in both groups. To improve median TSH levels (LI 3.6 mIU/l, TA 3.3 mIU/l) after crossover and 2nd titration, L-T_4 dosages were increased in 43% and 29% of patients on LI and TA L-T_4, respectively. Intention-to-treat analysis revealed similar median BS (LI 3, TA 2.0) and VAS (LI 8, TA 7.5) scores and median TSH (LI 6.1 mIU/l, TA 6.0 mIU/l) levels at the end of the study. After 12 months of L-T_4 treatment, 60% of subjects required a further increase in L-T_4 dosage, in both formulations, to adequately control hypothyroidism. At the end of the study, only the ThyPRO scales 'eyes', 'anxiety' and 'cosmetic complaints' had improved less on LI than on TA therapy. In conclusion this protocol was burdened by a high number of drop-outs; the number of data available may therefore constitute a limitation to the study. Both LI and TA L-T_4 formulations displayed similar efficacy. However, dosages need to be carefully increased when treatment for the control of hypothyroidism is started de novo. The tolerability of LI and TA L-T_4 proved similar and QoL improved in all patients on therapy.

DOI: 10.1530/endoabs.37.EP1058

EP1059

Serum Galectins are increased in patients with Graves' disease hyperthyroidism

Ana M Ramos-Leví[1,2], Ana Serrano[1], Miguel A Sampedro-Núñez[1], Alicia Vicuña[1], Ana Rodríguez-Muñoz[1], Rebeca Martínez[1], Hortensia De la Fuente[2,3] & Mónica Marazuela[1,2]
[1]Department of Endocrinology and Nutrition, Instituto de Investigación Princesa, Hospital Universitario Princesa, Madrid, Spain; [2]Universidad Autónoma de Madrid, Madrid, Spain; [3]Department of Immunology, Instituto de Investigación Princesa, Hospital Universitario Princesa, Madrid, Spain.

Introduction
Patients with autoimmune thyroid disease (AITD) exhibit aberrant immune-regulatory mechanisms. Galectins (Gal) are a family of glycan-binding proteins, which have been involved in immune regulation. However, the association of Gal with AITD remains unknown. In this study, we evaluated serum Gal-1 and Gal-9 in patients with AITD.
Methods
Peripheral blood samples from 31 patients with Graves' disease (GD) (14 with untreated hyperthyroidism, nine euthyroid with treatment, eight with iatrogenic hypothyroidism), 26 Hashimoto's thyroiditis (HT) (20 hypothyroid, six euthyroid with treatment), 12 non-GD hyperthyroid patients (NG) and 24 healthy controls were studied. Serum levels of thyroid hormones, thyroid antibodies (Ab), Gal-1 and Gal-9 were measured on the same day (FT4 by RIA; TSH, Tg-Ab, TPO-Ab and TSHR-Ab by immunoradiometric assays; Gal-1 and Gal-9 by ELISA). Patients were grouped according to clinical diagnosis and thyroidal status.
Results
Serum Gal-1 (ng/ml) and Gal-9 (pg/ml) were significantly increased in GD (3.756 and 8.582 respectively), HT (3.085, 9.188) and NG (2.822, 8.983), in comparison to controls (1.508, 7.323), $P<0.05$. No significant differences in Gal levels were found between the first three groups. Patients with hyperthyroidism (both GD and NG) had higher Gal-9 levels than euthyroid AITD patients, although there were no differences in Gal-1. In fact, in GD, we observed a direct correlation between Gal-9 and FT4 ($r=0.517$, $P=0.006$), and an inverse correlation between Gal-9 and TSH ($r=$-0.478, $P=0.007$). We did not find an association between Gal-9 and Ab levels in either group of AITD, although an association between Gal-1 and TPO-Ab levels was found in HT ($r=$-0.512, $P=0.038$). Antithyroid treatment reduced Gal-1 levels in patients with GD.
Conclusions
Galectins may be involved in the severity and pathogenesis of AITD, and could potentially be used as a diagnostic and therapeutic marker.
Disclosure
Grants form Fundación SEEN Award for Young Endocrinologists, FIS 13/1414 and PIE 13/41.

DOI: 10.1530/endoabs.37.EP1059

EP1060

Paraoxonase and arylesterase levels in autoimmune thyroid diseases

Hakan Korkmaz[1], Suzan Tabur[1], Mesut Özkaya[1], Elif Oguz[2], Nurten Aksoy[3] & Ersin Akarsu[1]
[1]Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology, Gaziantep University, Gaziantep, Turkey; [2]Faculty of Medicine, Department of Pharmacology, Harran University, Sanliurfa, Turkey; [3]Faculty of Medicine, Department of Clinical Biochemistry, Harran University, Sanliurfa, Turkey.

Objective
The aim of this study was to evaluate paraoxonase-1 (PON1) *activities and its association with oxidative stress status in* autoimmune thyroid disease (AITD).
Materials and methods
Patients with 25 Hashimoto thyroiditis (HT) and 25 Graves' disease (GD) and 27 healthy controls were enrolled in the study. Blood samples were obtained in euthyroid period and 3 months after the initiation of medical treatment. *S*erum samples from AIT diseases and healthy control group were analysed for paraoxanose (PON), arylesterase (ARE) activities, lipid hydroperoxide (LOOH) and total free sulfhydryl (–SH) levels.
Results
The preoperative PON and –SH levels of the patients with AIT were significantly lower compared to those of the control group ($P<0.001$, for each), while LOOH levels were significantly higher ($P<0.001$, for each). There was no significant difference between the patients with AIT and the healthy control groups in terms of ARE levels ($P>0.05$). PON levels showed a positive correlation with –SH ($r=0.522$, $P<0.001$) and a negative correlation with LOOH ($r=-0.487$, $P<0.001$).

Conclusion
Serum PON levels is decrease in patients with AIT, and serum PON is positively correlated with –SH, a well known antioxidant, and negatively correlated with LOOH, an oxidant.

DOI: 10.1530/endoabs.37.EP1060

EP1061

Reference values of TSH, FT_4 and FT_3 in a cohort of pregnant women in the north of Spain

David Ruiz Ochoa[1], María Piedra León[2], María del Carmen Baamonde Calzada[1], Fátima Mateos García[2], Azucena Setién Rodriguez[3], Cristina Temprano Marañon[3], Laura Gutierrez Chicote[4], Raquel Zubeldia Valdés[3], Rosa Nuria Secadas López[1], Sonia Ojugas Zabala[3], Mercedes Álvarez del Campo[3], Aurora Otero García[3], Iñigo Tejado Elviro[1] & Jose Antonio Amado Señaris[2]
[1]Sierrallana Hospital, Cantabria, Spain; [2]Marques de Valdecilla Universitary Hospital, Cantabria, Spain; [3]Department of Family Medicine, Health Care Center Area IV, Cantabria, Spain; [4]Department of Family Medicine, Health Care Center Area III, Cantabria, Spain.

Introduction
As soon as pregnancy is established, various physiological changes occur in maternal thyroid economy. Due to that, the reference limits of thyroid parameters used for the general population are no longer valid to diagnosis thyroid dysfunction during pregnancy.
Methods
We included 266 pregnant women, with no thyroid disorders and resident in Cantabria, a region in northern Spain. They were questioned about iodized salt and iodine supplements intake and blood samples for TSH, FT_4 and FT_3 were obtained in the first and third trimester of gestation and for TPO abs and Tg abs in the first trimester.
Results
Eighteen patients (6.76%) were TPO abs or Tg abs positive. Iodized salt was consumed by 39.8% in the first trimester and by 83.5% in the third ($P<0.01$) and iodine supplement by 70.7% in the first and 91.2% in the third ($P<0.01$). Reference values, expressed as median and 2.5 and 97.5 percentiles were: TSH 1.67 μUI/ml (0.27–4.16), FT_4 1.06 ng/dl (0.86–1.31), FT_3 2.97 pg/ml (2.42-3.65) in the first trimester and TSH 1.92 μUI/ml (0.57–4.01), FT_4 0.89 ng/dl (0.70–1.08), FT_3 2.85 pg/ml (2.24–3.51) in the third trimester. If we exclude TPO abs or Tg abs positive women from the analysis, reference values were: TSH 1.63 μUI/ml (0.27–4.13), FT_4 1.06 ng/dl (0.86–1.31), FT_3 2.97 pg/ml (2.42–3.64) in the first trimester and TSH 1.92 μUI/ml (0.65–3.95), FT_4 0.88 ng/dl (0.7–1.07), FT_3 2.85 pg/ml (2.27–3.53) in the third trimester. Difference between the first and third trimester were significant for TSH, FT_4 and FT_3 in both groups. The small group of women with positive TPO abs or Tg abs, presented a higher TSH in the first trimester compared with women without antibodies: TSH 2.23 μUI/ml vs 1.63 μUI/ml ($P=0.031$). No significant difference was found for TSH, FT_4 or FT_3 in relation to the consumption of iodized salt or iodine supplement, except a significantly higher FT_3 in the third trimester between women who take iodine supplements compared to women who did not ($P=0.045$).
Conclusions
Method-and gestation-specific reference ranges are needed to avoid misdiagnosis of thyroid function during pregnancy. Pregnant women with positive TPO abs or Tg abs show higher levels of TSH in the first trimester compared with women without antibodies.

DOI: 10.1530/endoabs.37.EP1061

EP1062

Serum prolactin and macroprolactin levels in pregnancy and association with thyroid dysfunction and thyroid autoimmunity

Metin Guclu[1], Soner Cander[1], Sinem Kiyici[1,3], Ebru Vatansever[2], Arif Bayram Hacihasanoglu[1] & Gürcan Kisakol[1]
[1]Department of Endocrinology, Sevket Yilmaz Research and Education Hospital, Bursa, Turkey; [2]Department of Biochemistry, Sevket Yilmaz Research and Education Hospital, Bursa, Turkey; [3]Department of Internal Medicine, Sevket Yilmaz Research and Education Hospital, Bursa, Turkey.

Aim
To assess the contribution of macroprolactin (macroPRL) to high serum prolactin (PRL) levels and association of prolactin and macroprolactin levels with thyroid status and thyroid autoimmunity during pregnancy.
Methods
Pregnant women ($n=138$) who had undergone a thyroid-stimulating hormone (TSH) screening during the first trimester of pregnancy enrolled in the study. Serum prolactin, macroprolactin, TSH, FT4, FT3, and thyroid autoantibodies were studied. Selected patients were divided into three groups; group 1 euthyroidsm (n 40: TSH between 0.1 and 2.5 μIU/l), group 2 hypothyroidism (n 54: TSH$\geqq$2.51 μIU/l), and group 3 hyperthyroid (n 44: TSH$\leq$0.09 μIU/l). The level of TPOAb $\geqq$35 U/ml has been considered as antibody positive. Polyethylene glycol (PEG) precipitation method was used for detection of macroprolactin and the percentage of monomeric prolactin recovery (monoPRL%) after PEG treatment 40% or less is considered as macroprolactinaemia.
Results
Macroprolactinaemia was found only in two patients (1.4%). One of these patients was euthyroid while the other one was hypothyroid and basal prolactin levels in these patients were 400 and 403 ng/ml respectively. Due to small number of macroprolactinaemia, percentage of their monoPRL recovery was used to compare prolactin homogeneity in other patients. Referring to the whole patients; there was no correlation between PRL, macroPRL or monoPRL% with thyroid hormone status and thyroid antibodies ($P>0.05$). A positive correlation was observed between the serum levels of PRL with TSH ($P=0.014$ and $r=0.219$), while negative correlation was found with FT4 ($P=0.011$ and $r=-0.227$).
Conclusions
There were no significant contributions of macroprolactin to prolactin levels during pregnancy. The levels of prolactin showed strong homogeneity and no correlation were found with thyroid dysfunction and thyroid autoimmunity at that time. This uncertainty persisted when correlation analyses done with monoPRL % instead of macroPRL. Eventually we couldn't find any relationship between thyroid hormones and antibodies with prolactin types in terms of molecular size.

DOI: 10.1530/endoabs.37.EP1062

EP1063

The effect of vitamin D on thyroid autoimmunity

Yasin Simsek[1], İlkay Cakir[2], Ferit Kerim Kucukler[1], Halit Diri[3], Murat Baglıcakoglu[1] & Serdar Guler[1]
[1]Endocrinology Department, Hitit University, Corum, Turkey; [2]Endocrinology Department, Bagcilar Goverment Hospital, Istanbul, Turkey; [3]Endocrinology Department, Mus, Mus Goverment Hospital, Turkey.

Introduction
Although, vitamin D (vit D) mainly regulates calcium and phosphate metabolisms, its deficiency may also contribute to the development of some carcinomas, autoimmune, and cardiac diseases. Vit D deficiency has been defined to correlate with increased autoimmune disease such as type 1 diabetes mellitus, rheumatoid arthritis, autoimmune thyroid diseases (AITD). Previous studies suggested that patients with AITD had lower vit D levels when compared with healthy controls. Moreover, vit D supplements were found to prevent the development and progression of autoimmune disorders such as type 1 diabetes mellitus and multiple sclerosis. Thus, we aimed to assess the effect of vit D on thyroid antibody titers in patients with AITD.
Materials and methods
Twenty-four participants were enrolled into the study. All of the participants were diagnosed with AITD and vit D deficiency. We assayed the serum anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) antibody levels before and a month after the vit D replacement. The daily dose of the vit D replacement was 2000 International Units (I.U).
Results
The AITD induced disorders in participants were as following: subclinical hypothyroidism: 66.6%, subclinical hyperthyroidism: 8.3%, overt hypothyroidism: 12.5%, and overt hyperthyroidism: 12.5%. Mean vit D level was 13.1$\pm$1.2 ng/ml. Before and after vit D replacement, anti-TPO titers were 276.6$\pm$42.7 IU/ml, 257.1$\pm$40.1 IU/ml ($P<0.001$); and anti-Tg titers were 371.9$\pm$64.3 IU/ml, 269.3$\pm$36.4 IU/ml ($P<0.001$) respectively. There was a statistically significant decrease in the anti-TPO and anti-Tg levels after the vit D replacement.
Conclusions
Vit D supplements seem to reduce thyroid antibody titers which play the main roles in the development and progression of AITDs. Therefore, vit D therapy may be used in the treatment of patients with AITD, particularly those with vit D

deficiency. Further studies are needed to assess the role of vitD replacement therapy in the treatment of autoimmune diseases.

DOI: 10.1530/endoabs.37.EP1063

EP1064

Endocrine involvement in systemic amyloidosis.

Ibtissem Oueslati[1], Nadia Khessairi[1], Ibtissem Ben Nacef[1], Nadia Mchirgui[1], Karima Khiari[1], Hayet Kaaroud[2] & Néjib Ben Abdallah[1]
[1]Department of Endocrinology, Charles Nicolle University Hospital, Tunis, Tunisia; [2]Department of Nephrology, Charles Nicolle University Hospital, Tunis, Tunisia.

Introduction
Systemic amyloidosis leads to functional compromise of various organs through infiltration of these tissues by amyloid protein.
The aim of this study was to determine the endocrine disorders in patients with systemic amyloidosis.
Methods
During the period from 1975 to 2006, we collected 580 patients with renal amyloidosis confirmed by histological exam. We selected 123 patients with hormonal exploration. 55 patients had thyroid function tests and 68 patients had adrenal function tests.
Results
There were 85 males and 38 females with a mean age of 49.6 ± 18 years.
Seventeen patients had primary hypothyroidism (30.9%) and ten patients had primary adrenal insufficiency (14.7%). The diagnosis of hypopituitarism was established in 18 patients with a central hypothyroidism in 14 cases and an adrenocorticotropic hormone deficiency in four cases. None of the patients had a simultaneous achievement of two pituitary abnormalities but one patient had TSH deficiency associated with adrenal insufficiency. Goiter was observed in nine patients with hypothyroidism in four cases.
All patients with adrenal insufficiency, ten patients with low TSH and five cases of goiter had AA amyloidosis.
Conclusion
Endocrine disorders such as hypothyroidism and adrenal deficiency were frequent in renal amyloidosis. Therefore their screening is necessary for an early treatment to improve patient's prognosis.

DOI: 10.1530/endoabs.37.EP1064

EP1065

Amyloid goitre as the first manifestation of systemic amyloidosis

Ibtissem Oueslati, Hana Ben Hadj Hassen, Ibtissem Ben Nacef, Nadia Mchirgui, Karima Khiari & Néjib Ben Abdallah
Department of Endocrinology, Charles Nicolle University Hospital, Tunis, Tunisia.

Introduction
Thyroid gland may be asymptomatically involved in most patients with secondary systemic amyloidosis. However, clinically detectable amyloid goiter is quite rare; often it is seen in patient with kidney involvement. We report one case of amyloid goitre without kidney manifestation.
Case report
A 30-year-old male diagnosed with bilateral bronchiectasis since 1992 was admitted with rapidly growing goiter associated with dysphagia for solids, change in voice, weight loss and dyspnea. The goitre was nodular large and hard. The rest of the examination was normal. His thyroid function tests were normal, antithyroglobulin and antimicrosomial antibodies were negatives. As he had signs of compression, total thyroidectomy was performed without complication. Histological exam showed type AA amyloid throughout the gland. Labial biopsy was positive for type AA amyloid. Evolution was favorable and 2 years later proteinuria was still negative.
Conclusion
We report perhaps, a new case of amyloid goitre without renal manifestation in the course of secondary amyloidosis. A preoperative diagnosis of amyloid goiter must be considered in patients with thyromegaly who have a predisposing risk factor for developing amyloidosis.

DOI: 10.1530/endoabs.37.EP1065

EP1066

A questionnaire on quality of life identifies Graves' ophthalmopathy patients who deserve more attention

Danilo Villagelin[1,2], Heloisa Nogueira[1], Ana Claudia Gomes Sandrin[1], Rebeca Carbinatto[1], Jakeline Gioyanetti[1], Larissa Campos[1], Roberto Santos[1], Natassia Bufalo[2], Joao Romaldini[1] & Laura Ward[2]
[1]Pontificia Universidade Católica de Campinas, Campinas, Brazil; [2]GEMOCA – Laboratory of Cancer Molecular Genetics, University of Campinas, Campinas, Brazil.

Introduction
Graves' ophthalmopathy (GO) varies from minor changes to visible face disfigurement which may compromise the visual capacity and the aesthetics of the patient. These deformities affect the quality of life in both functional and emotional senses. There are some questionnaires designed to evaluate the patient's health, quality of life and relationship with a specific disease. The use of these questionnaires is recommended to improve the quality of care and, mainly, to identify patients who are in need of psychological support. However, they need to be validated in each country.
Methods
We evaluated 140 consecutive Brazilian GD patients investigating the severity of their ophthalmopathy (Clinical Activity Score), and quality of life, according to the questionnaire on quality of life in Graves' ophthalmopathy (GO-QoL).
Results
The patients were divided in two groups according their initial CAS. Group 1 (CAS 0 or 1), $n = 108$, and group 2 (CAS > 2), $n = 32$. There were no differences in age, duration of disease and gender between the groups. However, group 1 had better results concerning the score of total visual functioning ($P < 0.005$) and the score of total appearance ($P < 0.0001$); patients in group 2 were more affected on simple tasks such as moving around the house ($P < 0.05$), walking outdoors ($P < 0.005$), reading ($P < 0.05$), watching TV ($P < 0.005$). In addition, this group had a worse score on self-confidence ($P < 0.0001$) and felt hindered from doing something they wanted to do because of GO ($P < 0.05$).
Conclusion
GO significantly affects the quality of life and the use of the GO-QoL questionnaire permitted to identify patients who deserve specific attention.

DOI: 10.1530/endoabs.37.EP1066

EP1067

Abstract withdrawn.

DOI: 10.1530/endoabs.37.EP1067

EP1068

Graves' disease and HIV infection: bad response to antithyroid drugs due to interaction with HIV therapy

Catarina Moniz[1], Maria José Campos[2] & Carlos Vasconcelos[1]
[1]Endocrinology Department, Hospital de Egas Moniz, CHLO-EPE, Lisbon, Portugal; [2]Infectiology Department, Hospital de Egas Moniz, CHLO-EPE, Lisbon, Portugal.

Graves' disease is one of the multiple autoimmune diseases that have been reported in HIV-infected patients. With the upsurge of highly active anti-retroviral therapy (HAART) the incidence of autoimmune diseases in HIV-infected patients is increasing, especially after immune reconstitution. We present a male, 51-year-old, who started complaining with anxiety, sudoresis and palpitations. The laboratory workout revealed hyperthyroidism: TSH <0.02 μU/ml (0.46–4.68), FT4 28 pmol/l (10.0–28.2), FT3 13.7 pmol/l (4.26–8.10). The patient started propylthiouracilo 100 mg per day and was referred to the Endocrinology Department. He had Mitral Insufficiency and HIV-1 infection. He was on HAART since 2007 with emtricitabin, tenofovir, atazanavir and ritonavir. The etiologic study disclosed Graves disease with TRAbs level 45.3 U/l (<1). We changed propylthiouracilo for thiamazole. During follow-up most of the time it wasn't possible to achieve euthyroidism. We offered other therapeutic options (Iodine-131 or surgery) but the patient rejected them. On the 23rd month of thiamazole therapy the patient was icteric and blood workout revealed hyperbilirubinemia (total bilirubin 8.1 mg/dl), FT4 48.1 pmol/l and FT3 18.7 pmol/l. We discussed these results with the Infectiology Department and hyperbilirubinemia was interpreted as an atanavir adverse effect. Boosted atazanavir (with ritonavir) was replaced by rilpivirine and we maintained the same dosis of thiamazole (15 mg per day). 6 weeks later he had normal total bilirunin (0.64 mg/dl) and normal/low thyroid hormones: FT4 9.45 pmol/l and FT3 6.05 pmol/l. Both atazanavir, ritonavir and thiamazole are metabolized in cytochrome P450. In this case the interaction resulted in decreased benefit of thiamazole and explains why it was so difficult to attained euthyroidism. To the best of our knowledge this is the first time the interaction between atazanavir and thiamazole is reported.

DOI: 10.1530/endoabs.37.EP1068

EP1069

Abstract withdrawn.

DOI: 10.1530/endoabs.37.EP1069

EP1070

Plasma visfatin/pre-B-cell colony enhancing factor levels in hypothyroid patients and relationship of these levels with thyroid autoimmunity and atherosclerosis

Bekir Ucan[1], Nur Kebapci[2], Sema Uslu[2], Mehmet Kara[2], Belgin Efe[2] & Setenay Oner[2]
[1]Ministry of Health, AIBU Izzet Baysal Medical Faculty Training and Research Hospital, Bolu, Turkey; [2]Osmangazi University Medical Faculty, Eskisehir, Turkey.

Visfatin/pre-B-cell enhancement factor is an adipocytokine, which is found in the visceral fat tissue and enhances the growth of precursor of B cells through showing synergy with IL7 and stem cell factors. Other cytokines released from the adipose tissue are TNFα and IL6, which has been shown to be related with pathogenesis of insulin resistance, diabetes, dyslipidaemia, inflammation, and atherosclerosis. Our aim was to determine the relationship of plasma visfatin/pre-B-cell colony enhancing factor levels with thyroid autoimmunity and atherosclerosis. The study was performed randomly on 35 patients (32 women/three men, mean age 43.8 ± 9.6 years) diagnosed with Hashimoto's thyroiditis and 18 healthy controls (17 women/one men, mean age 43.3 ± 5.2 years) attending our outpatient clinic between June 2009 and January 2010. Before therapy anthropometric levels, carotid intima–media thickness (CIMT), serum anti-Tg, anti-TPO, hsCRP, homocystein, lipo(a), ApoA, ApoB1, β-2 microglobulin, insulin, glucose, visfatin, IL6, TNFα, oxidized-LDL levels, and lipid profile was measured. Plasma visfatin oxidised LDL, IL6, and TNFα levels did not differ from the control group before and after therapy in hypothyroid patients, statistically. The cardiovascular risk factors like systolic and diastolic blood pressure, HOMA-IR index, triglyceride, Apo B and ApoB/ApoA, homocystein, β-2 microglobulin, and CIMT were found to be elevated in the patients. Ox-LDL, cholesterol, homocysteine, and proteinuria levels were positively correlated with anti-Tg levels. Conclusionally, we think that non-traditional CVD risk factors are elevated in hypothyroid Hashimoto's thyroiditis patients and as a atherosclerosis indicator CIMT increase accompanies it and anti-Tg antibody is a bridge between autoimmunity and atherosclerosis.

DOI: 10.1530/endoabs.37.EP1070

EP1071

Could thyroid replacement therapy not be enough to reduce oxidative stress in hypothyroid patients with Down' syndrome? A cohort study

Emanuele Rocco Villani[1], Graziano Onder[1], Angelo Carfì[1], Francesco Pagano[1], Sebastiano Raimondo[2], Chantal Di Segni[2], Andrea Silvestrini[3], Elisabetta Meucci[3] & Antonio Mancini[1]
[1]Department of Internal Medicine and Geriatrics, Catholic University of Sacred Heart, Rome, Italy; [2]Division of Endocrinology, Department of Medical Sciences, Catholic University of Sacred Heart, Rome, Italy; [3]Institute of Biochemistry and Clinical Biochemistry, University of Sacred Heart, Rome, Italy.

Hypothyroidism and autoimmune thyroiditis are common in patients with Down' syndrome (DS), leading to common prescription of thyroid replacement therapy. On the other hand, thyroid function is involved in oxidative stress (OS) mechanisms. DS is a well-known high OS condition because several genes involved in OS mechanisms map on chromosome 21 and coenzyme Q10, lipophilic antioxidant, could be more correlated with hypothyroidism than TSH in DS people. To investigate relationships among thyroid function, OS and replacement therapy, we enrolled 26 adults with DS (ten males) aged 18–64. Fourteen were under thyroid replacement therapy with levothyroxine. A fasting blood plasma sample was collected at 0900 h and TSH (NR 0.30–2.80 μUI/l), fT_4 levels and total antioxidant capacity (TAC) were evaluated. TAC was evaluated with colorimetric method, using the system metamyoglobin–H_2O_2 and the chromogen ABTS; the latency time (LAG, s) in the appearance of ABTS radical proportional to antioxidant content of the system. Patients were classified in two groups: i) patients under thyroid replacement therapy (14/26) and ii) patients without replacement therapy (12/26). Among the first group, 57% (8/14) of patients were euthyroid (mean ± s.d. TSH 3.01 ± 3.27), whilst 42% (5/12) were hypothyroid in the second group (mean TSH 2.39 ± 1.09). TAC was lower in the first group (62.50 ± 14.64) than in the second group (74.17 ± 12.40), regardless of TSH level. These data confirm hypothyroidism as a high OS condition and suggest that replacement therapy alone could not be enough to establish normal TAC levels in hypothyroid patients. Further studies will be necessary to evaluate whether a supplementation with antioxidants should be considered in DS hypothyroid patients, due to the competence of two causes of high oxidative stress in those patients. It could also be necessary to evaluate whether non-DS hypothyroid patients under thyroid replacement therapy show higher OS levels.

DOI: 10.1530/endoabs.37.EP1071

EP1072

Hypothyroidism and the haemodialysis patients: it is a matter for discussion

Mohammed Aljefery
Merjan Teaching Medical City, Hilla, Babylon, Iraq.

149 haemodialysis chronic renal failure (CRF) patients on haemodialysis (HD) program of 4 h/three times a week investigated for thyroid gland function and try to answer the question: is the thyroid function abnormality affect the response of the haemodialysis CRF patients response to recombinant human erythropoietin (rHuEPO)? We compare the results of the thyroid gland markers; T_3, T_4, and TSH (which tested by minividus technique) of the patients with the packet cell volume (PCV) values of the patients and showed if the haemodialysis CRF with hyper or hypothyroidism affect the response of the patients to the rHuEPO and if there are differences in the values of the PCV between the groups of the patients after fixed the duration and the times of the HD session and the same dose and route of the rHuEPO. The results analysed statistically and discussed and from that we can concluded there are hyporesponsiveness of the rHuEPO in patients with CRF and hypothyroidism in haemodialysis and for this reason we advise to search any haemodialysis patients for thyroid function.

DOI: 10.1530/endoabs.37.EP1072

EP1073

The changes of thyroid function after coronary angiography in Koreans

Dong Sun Kim[1], Jung Hwan Park[1], Yeon-Ah Sung[2] & Kyu Chang Won[3]
[1]Department of Internal Medicine, College of Medicine, Hanyang University, Seoul, Republic of Korea; [2]Department of Internal Medicine, College of Medicine, Ewha Womans University, Seoul, Republic of Korea; [3]Department of Internal Medicine, College of Medicine, Yeungnam University, Gyeongbuk, Republic of Korea.

Background
The risk of iodine-induced thyrotoxicosis is increased in patients with Graves' disease and multi nodular goiter with thyroid autonomy. At same time, hypothyroidism can develop after iodine exposure in patients with Hashimoto's thyroiditis. But, there are no studies about the influence of iodine containing contrast media on thyroid function in iodine excessive area. This study was done to evaluate the changes of thyroid function after coronary angiography (CAG) with/without percutaneous coronary intervention (PCI) (CAG ± PCI) in Koreans with excessive iodine intake.
Methods
56 subjects with normal thyroid function who admitted for CAG ± PCI were enrolled. Levels of TSH and free thyroxine (FT_4) in serum were measured before CAG ± PCI and at 1 and 12 weeks after CAG ± PCI.
Results
There was no statistical significance of levels of TSH measured between before CAG ± PCI and at 1 and 12 weeks after CAG ± PCI. Levels of FT_4 were not changed before and after CAG ± PCI, but mild increase of FT_4 was observed at 1 week after CAG ± PCI. Larger amount of iodine containing contrast media for PCI did not change the thyroid function either. Among the 56 subjects, three patients were newly diagnosed as subclinical hypothyroidism at 1 week after CAG with PCI. Among the three patients, one patient remained subclinical hypothyroidism at 12 weeks after CAG with PCI.
Conclusion
There were no changes of thyroid function after CAG in Koreans with normal thyroid function. Mild elevations of FT_4 levels at 1 week after CAG ± PCI was showed, but it normalised at 12 weeks after CAG ± PCI. This suggests that there was no significant effect of iodine containing contrast on thyroid function.

DOI: 10.1530/endoabs.37.EP1073

EP1074

Clinical and social concerns in treated patients with primary hypothyroidism in Basrah: a cross sectional study

Haider Ayad Yassin Yassin, Alaa Khattar Musa Musa & Abbas Ali Mansour
Basrah College of Medicine, Basrah, Iraq.

Background
Despite available treatment for hypothyroidism, levothyroxine replacement therapy in a biochemically appropriate dose does not necessarily relieve patients' symptoms and complaints. The aim of the study was to evaluate the concerns of patients treated with hypothyroidism and to correlate these concerns with different patient characteristics and thyroid biochemical control.
Method
One hundred and eighteen treated primary hypothyroid patients attending Al-Faiha Diabetes Endocrine and Metabolism Center (FDEMC) in Al-Basrah were entering a questionnaire designed to capture personal, anthropometric, biochemical, and clinical data. Twenty-four concerns were questioned to the patients who score these concerns on a four point Likert scale.
Results
The most scored patients' concerns were fatigue, neuropathic pain, lack of weight loss, cold intolerance, breathing problems, and swallowing problems. No statistically significant relations were existed between these concerns and TSH control, except for a high TSH group which were highly likely to have concerns of feeling sick (OR: 0.27, 95% CI 0.54–2.0, $P=0.001$), neuropathic pain (OR: 0.4, 95% CI 0.17–1.6, $P=0.01$), cold intolerance (OR: 0.35, 95% CI 0. 0.3–1.7, $P=0.005$), and hair problems (OR: 0.26, 95% CI 0.6–2.1, $P<0.0001$). While they were less likely to have concerns about lack of weight loss (OR: 8.7, 95% CI -2.9 to -1.3, $P<0.0001$) and permanent medication (OR: 2.7, 95% CI -1.8 to -0.35, $P=0.003$) than in normal TSH patients where these concerns scored more and significantly. A significant correlation existed between duration of the hypothyroidism and patients' concerns of swelling of the hands and feet ($R=0.7$, $P<0.0001$), memory problems ($R=0.4$, $P<0.0001$), hearing disturbance ($R=0.38$, $P<0.0001$), and hair problems ($R=0.3$, $P=0.001$). Age significantly affect patients concerns of memory problems ($R=0.6$, $P<0.0001$), swelling of the hands and feet ($R=0.4$, $P<0.0001$), and hearing disturbance ($R=0.37$, $P<0.0001$). Positive correlation was present between LDL cholesterol level and patients' concerns of cold intolerance ($R=0.3$, $P=0.001$), hair problems ($R=0.28$, $P=0.003$), feeling sick ($R=0.2$, $P=0.02$), and neuropathic pain ($R=0.18$, $P=0.04$). The total cholesterol level also showed a positive correlation with patients' concerns of cold intolerance ($R=0.3$, $P=0.001$), hair problems ($R=0.25$, $P=0.01$), neuropathic pain ($R=0.22$, $P=0.01$), and fatigue ($R=0.2$, $P=0.04$).
Conclusion
We cannot rely on the TSH level alone as a marker of optimal treatment outcome in patients with primary hypothyroidism because it does not reflect the concern status of the patients.

DOI: 10.1530/endoabs.37.EP1074

EP1075

Ultrasonographical and cytological features of exophytic thyroid nodules: do exophytic nodules pretend to be malignant?

Fatma Dilek Dellal[1], Husniye Baser[1], Didem Ozdemir[2], Aydan Kilicarslan[3], Reyhan Ersoy[2] & Bekir Cakir[2]
[1]Department of Endocrinology and Metabolism, Ataturk Education and Research Hospital, Ankara, Turkey; [2]Department of Endocrinology and Metabolism, School of Medicine, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey; [3]Department of Pathology, School of Medicine, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey.

Aim
Exophytic nodule refers to a nodule that sticks out of the normal thyroid boundary/outline. Other definition is a nodule with an acute angle between the lesion and adjacent thyroid capsule. In the literature, one study reported that thyroid nodules with exophytic configuration showed a high malignancy rate. We aimed to compare ultrasonographical features and cytopathologic results of exophytic and non-exophytic thyroid nodules.
Material and method
Thirty-four exophytic and 34 non-exophytic thyroid nodules in which fine-needle aspiration biopsy was indicated throughout 3 months were evaluated prospectively. Mean nodule size was similar in two groups (18.83 ± 8.71 and 15.28 ± 7.57 mm, $P=0.173$). The ratio of presence of peripheral hypoechoic halo and marginal irregularity was also similar in both group ($P=0.512$ and $P=0.153$ respectively). Microcalcification was present in 21.4 and 29.4% of exophytic and non-exophytic nodules respectively ($P=0.424$). Macrocalcification was detected in 4.5% of exophytic and 11.8% of non-exophytic nodules ($P=0.111$). 47.6% of exophytic nodules was hypoechoic and 52.4% was isoechoic. 47.1% of non-exophytic nodules was hypoechoic and 52.9% was isoechoic. Color flow Doppler pattern was defined as non-vascular, peripheral, central, or of mixed type and was similar in both groups ($P=0.138$). Cytopathologic results of exophytic nodules were 75% benign, 4.3% follicular lesion or atypia with undetermined significance, 2.3% suspicious for malignancy, 2.3% malign, and 15.9% non-diagnostic. In non-exophytic group, 79.4% was benign and 20.6% was non-diagnostic ($P=0.497$).
Conclusion
Exophytic configuration of thyroid nodules was rarely investigated as a possible predictive feature for malignancy in the literature. In this study, we did not find any difference in terms of ultrasonographical features and cytological results between exophytic and non-exophytic thyroid nodules. However, more comprehensive studies are needed to clarify any possible relation between exophytic configuration and malignancy.

DOI: 10.1530/endoabs.37.EP1075

EP1076

Dynamics of thyroid function tests during antiviral treatment of hepatitis C

Olga Nechaeva, Alexander Dreval, Maria Matsievich, Maria Petrachenkova, Kseniya Kokina & Pavel Bogomolov
Moscow Regional Research Clinical Institute, Moscow, Russia.

Aim
To estimate the frequency of changes in thyroid function on the background of antiviral therapy in patients with chronic hepatitis C.
Material and methods
The retrospective group was consists of 204 patients (mean age 35.5 ± 8.4 years) with HCV genotype 3a, who took the antiviral therapy course with pegylated

interferon and ribavirin during 24 weeks. The patients were divided for two groups: 86.3% (176) had a sustained virological response (SVR), 13.7% (28) did not reach the SVR. SVR was defined as undetectable HCV RNA level at weeks 4–12. The groups were matched only by sex, because of the mean age of patients with SVR was statistically significant younger (32.3±7.2 years) than patients without SVR (40.63±8.66 years).

Results

Among 204 patients, TSH, fT_4, and TPOAb levels were analysed in 66 patients before and after treatment. 92.4% (61) subjects had TSH level between 0.4 and 4.0 mIU/l with normal fT_4. 7.6% (5) subjects had subclinical hypothyroidism. Although, absolute levels of TSH, fT_4, and TPOAb were not significantly different before and after treatment, however, after course number of people with normal TSH level decreased to 71.2% (47), and in 28.8% (19) patients thyroid dysfunction was diagnosed. Most of them became hypothyroid and Graves' disease manifested only in one case. In patients with normal function tests before treatment there was no difference in levels of fT_4 in groups with SVR+ and SVR− and there was the significant difference in levels of TSH and TPOAb: the lower the value of TSH and TPOAb was before treatment, the more marked presence of SVR was determined.

Conclusion

Antiviral treatment can caused a statistically significant change in the thyroid function in 21.2% patients. The levels of TSH and TPOAb before treatment may be a predictor of SVR. Another study are necessary for confirming this fact.

DOI: 10.1530/endoabs.37.EP1076

EP1077

Nondiagnostic fine-needle aspiration biopsy results: our clinic experience

Sevilay Ozmen[1], Ilknur Calik[1], Ebru Sener[1], Esref Kabalar[1], Ozge Timur[2], Hakan Sevimli[2], Ayse Carlioglu[3] & Senay Arikan Durmaz[3]
[1]Department of Pathology, Training and Research Hospital, Erzurum, Turkey; [2]Department of Internal Medicine, Training and Research Hospital, Erzurum, Turkey; [3]Department of Endocrinology, Training and Research Hospital, Erzurum, Turkey.

Adequacy of thyroid fine-needle aspiration (FNA) is generally defined by the thyroid follicle cells, amount, and quality of colloid. Samples priorly should be evaluated for adequacy. A set of qualifying criteria are specified in Bethesda system to remove subjectivity from the adequacy assessment. Each sample prepared from a thyroid FNA should be monitored at least six follicles cell groups containing at least ten cells. In addition to these criteria of assessing the adequacy, the quality of preparation is also very important. Follicular cells should able to observe, the blood or clots should not cover the preparation and painting should be made fine. Our clinic evaluation results of FNA biopsy (FNAB) are reported as non-diagnostic for 69 patients; 54 females and 13 males. All the patients reported as non-diagnostic were operated without re-biopsy. As these patients evaluated after operation 57 of them; 44 females and 13 males diagnosed as nodular goitre (81.5%), four adenomatous hyperplasia (7%), one diffuse hyperplasia (1.8%), one papillary carcinoma (1.8%), three follicular adenoma (5.4%), and one Hürthle cell adenoma (1.8%). Patients with non-diagnostic FNAB results evaluated after operation with histopathological preparations and reported 96.4% benign and 3.6% malignant. Most of the nodules with non-diagnostic/inadequate FNAB evaluated as benign. These results bring a question to mind; should these patients operated immediately? As Bethesda's clinical approach, patients with non-diagnostic FNAB should be re-aspirated after 3 months. To avoid false positive results depending on regeneration, there must be at least 3 months between two aspirations. We believe such an approach would protect patients from unnecessary surgery.

DOI: 10.1530/endoabs.37.EP1077

EP1078

False negatives and reasons: Erzurum Research and Training Hospital Pathology Department experience

Sevilay Ozmen[1], Ilknur Calik[1], Senay Erdogan[1], Ozge Timur[2], Hakan Sevimli[2], Ayse Carlioglu[3], Senay Arikan Durmaz[3] & Fazli Erdogan[1]
[1]Department of Pathology, Training and Research Hospital, Erzurum, Turkey; [2]Department of Internal Medicine, Training and Research Hospital, Erzurum, Turkey; [3]Department of Endocrinology, Training and Research Hospital, Erzurum, Turkey.

Fine-needle aspiration biopsies (FNAB), adequate for examination, reported as benign re-evaluated with histopathological samples. 61 patients, 52 females and nine males re-evaluated. 41 of them reported as benign. 20 of the patients, seven females and three males reported as papillary carcinoma. Six of the papillary carcinomas were single focus, two muiticentric, and 12 papillary microcarcinoma. Six of the eight patients malignant lobe was different from the lobe that FNA was made. Multicentric malignancy was detected in two cases. Malignant FNA diagnosis forms 4–8% of all thyroid FNAs, as in literature. Most of them are papillary thyroid carcinoma (PTC). In fact PTC cytopathological features are quite obvious, at the level of diagnostic. Patients diagnosed PTC with FNAB showed PTC at the rate of 96–100% with histopathological samples. However, false-negative value was 32.78% in our patients under observation. This value is over the false-negative rate ranging between 1 and 21.3% stated in the literature. However, the results of the histopathological report with the results of cytopathological reports examined in detail the majority of the cases with false-negative study (60%) constitute papillary microcarcinoma. This finding suggests that PTC is overlooked with FNAB. Our false-negative rates are compatible with the literature as PTC excluded. Another reason for our false-negative value is the patchy distribution of PTC in the same nodule. As a result, FNAB accompanied with ultrasound, should be applied to all solid, hypoechoic nodules and nodules with microcalcification. Also, because of the presence of PTC showing a patchy distribution in a single nodule, multiple biopsies should be taken from more than one areas, from the large nodules seen sonographically suspicious.

DOI: 10.1530/endoabs.37.EP1078

EP1079

Multiple disease associations in autoimmune polyglandular syndromes

Anna Dabrowska[1], Agnieszka Zwolak[1,2] & Jerzy Tarach[1]
[1]Chair and Department of Endocrinology, Medical University of Lublin, Lublin, Poland; [2]Chair of Internal Medicine, Department of Internal Medicine in Nursing, Medical University of Lublin, Lublin, Poland.

Introduction

Autoimmune polyglandular syndromes (APS) are a heterogeneous group of disorders characterised by autoimmune activity against endocrine and non-endocrine organs. APS type depends on the combination of the diseases (APS1, APS2, and APS3).

Methods

The study was conducted in 89 patients (70F and 19M) with APS aged mean 50.00±14.80 years, treated at Endocrinology Department between 2003 and 2015. We analysed clinical manifestations, results of laboratory tests and imaging to determine the components of APS.

Results

The most common syndrome was APS3 (69.66%). 24.72% of patients had APS2, only five subjects (5.62%) suffered from APS1. Autoimmune thyroid disease was found in 84.27% of cases, i.e. Hashimoto's thyroiditis (58.43%) and Graves's disease (25.84%), and in 100, 86.36, and 82.26% of APS1, APS2, and APS3 cases respectively. Type 1 diabetes had been diagnosed in 61.80% of participants (in 20.00, 27.27, and 77.42% of APS1, APS2, and APS3 cases respectively). Besides patients with APS2, all subjects with APS1 were treated due to Addison's disease which was found in 29.21% of APS patients. Other problems such as: vitiligo (17.98%), psoriasis (12.36%), Addison-Biermer anemia (10.12%), alopecia areata (5.62%), asthma (3.37%) and in individuals – rheumatoid arthritis, myasthenia gravis, coeliac disease, ulcerative colitis, and autoimmune hepatitis were observed. In APS1, three to six diseases were noted, mostly the coexistence of Addison's disease and hypoparathyroidism. Two to three diseases were found in APS2. Schmidt's syndrome was determined in 63.64% of patients with APS2, Carpenter syndrome only in two cases. The most common diseases in APS2 were: Hashimoto's disease, type 1 diabetes, Graves's disease (72.73, 27.27, and 13.64% respectively). In APS3, two to four diseases were found. Type 1 diabetes, Hashimoto's disease, and Graves' disease were the most common disorders (77.42, 50.00, and 32.26% respectively). The most common coexistence in APS3 was type 1 diabetes with Hashimoto's disease.

Conclusions

Although, some diseases occur more frequently than others, it should be remembered about various APS components during follow-up such patients.

DOI: 10.1530/endoabs.37.EP1079

EP1080

Intraocular pressure, corneal, and retinal thickness in patients with euthyroid autoimmune thyroiditis

Fatma Neslihan Cuhaci[1], Husniye Baser[2], Nagihan Ugurlu[3], Fatma Yulek[3], Reyhan Ersoy[1], Nurullah Cagil[3] & Bekir Cakir[1]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Yildirim Beyazit University, Ankara, Turkey; [2]Department of Endocrinology and Metabolism, Ataturk Education and Research Hospital, Ankara, Turkey; [3]Department of Ophthalmology, Ataturk Education and Research Hospital, Ankara, Turkey.

Introduction
Ocular changes and ocular symptoms may be encountered in patients with hypothyroidism and hyperthyroidism. However, the data concerning the effects of thyroid disorders on intraocular pressure (IOP), central corneal thickness (CCT), and retinal thickness (RT) are very rare. Here, we aimed to evaluate the alterations in IOP, CCT, and RT in patients with euthyroid autoimmune thyroiditis (AIT).
Methods
Twenty-five subjects with euthyroid AIT were included into the study. The patients were compared with age and sex-matched 40 healthy subjects. A detailed ophthalmologic examination including the IOP, CCT, and RT was performed in both groups.
Results
There was no statistically significant difference in mean right RT, left RT, right CCT, and left CCT between two groups ($P>0.05$ for all parameters). Also, no significant difference was found between groups concerning right and left IOP ($P>0.05$ for all parameters). In patients groups, left RT was significantly higher in patient with TSH >2.5 μIU/ml than those of TSH <2.5 μIU/ml (294.85 ± 23.58 μm vs 261.50 ± 21.70 μm, $P=0.003$). A positive correlation was observed between left RT and TSH levels ($r=0.269$, $P=0.033$). No significant correlation was found between free triiodothyronine levels, and right CCT, right RT, right IOP, left CCT, left RT, and left IOP levels ($P>0.05$ for all parameters). Also, free tetraiodothyronine levels were not significantly correlated with right CCT, right RT, right IOP, left CCT, left RT, and left IOP levels ($P>0.05$ for all parameters).
Conclusion
An increase in IOP in Graves' ophthalmopathy is a well-known entity. In literature, hypothyroidism seems to cause a reversible increase in CCT and IOP. In this study, we observed no significant difference between groups concerning IOP, CCT, and RT. So, further studies with larger sample size are needed to evaluate IOP, CCT, and RT in patients with euthyroid AIT.

DOI: 10.1530/endoabs.37.EP1080

EP1081

Should fine-needle aspiration biopsy perform all of nodules in patients with nodular goitre?

Sevilay Ozmen[1], Ilknur Calik[1], Hilal Balta[1], Ozge Timur[2], Ayse Carlioglu[3], Hakan Sevimli[2], Senay Arikan Durmaz[3] & Ali Kurt[1]
[1]Department of Pathology, Training and Research Hospital, Erzurum, Turkey; [2]Department of Internal Medicine, Training and Research Hospital, Erzurum, Turkey; [3]Department of Endocrinology, Training and Research Hospital, Erzurum, Turkey.

Introduction and aim
Fine-needle aspiration (FNA) biopsy has become widely accepted as a reliable method for diagnosis of malign thyroid nodule. In our study we aimed to review results of thyroid FNA biopsy to be performed by same endocrinologist and compared to their histopathological results after thyroidectomy.
Materials and methods
This retrospective study was done at the department of pathology for a period of 2 years from 2012 to 2014. The 401 patients applied to our Endocrinology Department due to solitary or multinodular goitre was included the study. Ultrasonography guide was used in all of FNA. FNA findings according to Bethesda classification were compared with corresponding histopathology findings, obtained with thyroidectomy specimens.
Results
After thyroidectomy, we determined that eight women (mean age 50.7 ± 6.8 years) of 401 patients with nodular goitre had papillary thyroid cancer in a cross thyroidal lob which FNA was not made, although finding of FNA was benign at one thyroid lob which FNA was made. Moreover, multicentric papillary thyroid cancer was found in two of them after thyroidectomy.
Conclusions
Our landmark finding point out that FNA should be performed all of suspicious nodule rather than dominant nodule. On the other hand multicentric papillary thyroid cancer are still a problem, although, FNA is widely used for evaluate cytology of nodules.

DOI: 10.1530/endoabs.37.EP1081

EP1082

Hyperthyroidism in Internal Medicine Services in Spain (2005–2012)

Sandra Duran[1], Judith Lopez[2], Ana Ortolá[1], Irene Crespo[1], Teresa Ruiz Gracia[1], Manuel Mendez[1], Karla Nuñez[1] & Javier Marco[1]
[1]Hospital Clinico San Carlos, Madrid, Spain; [2]Hospital Universitario de Canarias, San Cristobal de la Laguna, Spain.

Introduction
The prevalence of hyperthyroidism in patients admitted in Internal Medicine at Spanish hospitals is 0.8%. Proper diagnosis and management of HTD in these patients is still a challenge and therefore, the analyses of the factors involved in the prognosis and survival is of interest.
Methods
Data from the minimum-data-set (MDS) of Spanish National health System were collected during 2005–2012 from discharged patients of Internal Medicine with HTD diagnosis. A bivariate analysis was performed in order to detect differences in the mortality rate, median age, median hospital stay, readmission rate and comorbidities among HTD and non HTD (NHTD) patients. A logistic regression analysis was performed using as dependent variable in-hospital mortality and sex, mean age, adjusted comorbidities measured by the Charlson's index and HTD as independent variable. χ^2 and Student's t-test were performed. SPSS22.
Results
A total of 32 515 out of 3 952 018 (0.8%) cases of HTD were found with a 66% of women vs 47.1% in NHTD ($P<0.001$). Mean age was 77 (S.D. 12.71) years vs 72 (S.D. 17.06) in NHTD. Atrial fibrillation was more common in HTD (41% vs 22%; $P<0.001$), and heart failure was more frequent in HTD (33% vs 21%; $P<0.0001$). The mortality rate in HTD was lower than in NHTD (8% vs 10%; $P<0.001$). In the logistic regression analyses adjusted by age, sex, and Charlson's corimbility index, HTD was found to be an independent factor to prevent mortality in inpatients OR 0.69 (CI: 0.66–0.74; $P<0.0001$).
Conclusions
HTD patients admitted to Internal Medicine wards have a lower mortality than NHTD. The frequency of women, atrial fibrillation and heart failure was higher in the HTD group. It is still unknown why HTD patients show lower mortality during admission. Perhaps other clinical and therapeutical factors, which have not been assessed through this retrospective study, have been involved with the hospital prognosis.

DOI: 10.1530/endoabs.37.EP1082

Endocrine tumours

EP1083

The prevalence of hyponatraemia and mortality in lung cancer patients

Ankit Jain, Alam Salma, Sophie Mascall, Shobhit Baijal, Joyce Thompson & Jayadave Shakher
Birmingham Heartlands Hospital, Birmingham, UK.

Aim
To estimate the prevalence and clinical significance of hyponatraemia in patients with lung cancer.
Methods
The data were obtained from Hospital Registry. The serum sodium (SNa) on diagnosis was used for statistical comparisons. Normonatraemia is defined as SNa 135–144 mmol/l, hyponatraemia <135 mmol/l, and hypernatraemia >145 mmol/l. The data was analysed for small cell (SCLC), non-small cell (NSCLC) and unknown group where histological diagnosis was not possible due to clinical reasons. Data analysis by STATA, version 12.1.
Results
The study population was 314 (57.3% males and 42.7% females). There were 16.4% SCLC, 60.1% NSCLC, and 23.5% unknown group. The sex distribution in SCLC – 52.9% males and 47.1% females, NSCLC – 59.4% males and 40.6% females, and unknown – 56.2% males and 43.8% females. The mean age in SCLC $69.1+10.2$, NSCLC $69.7+9.7$, and unknown $70.3+13.8$ ($P=0.84$). The overall incidence of hyponatraemia, SNa <135 mmol/l was 37.6%. The incidence of hyponatraemia was higher in SCLC than other two groups but not statistically significant ($P=0.09$) (SCLC 49.0%, NSCLC 33.2%, and unknown 41.1%).

Analysis according to severity of hyponatraemia between groups. Normonatraemic (135–144) 60.5%, mild (130–134) 21.7%, moderate (120–129) 15.3%, severe (<120) 0.6%, and hypernatraemia (≥145) 1.9%. Distribution of hyponatraemia among groups were as follows: SCLC mild 27.5%, moderate 21.6%, and severe 0% ; NSCLC: mild 19.8%, moderate13.4%, and severe 0%. The risk of death within 30 days was 43% higher in the hyponatraemic group than the normonatraemic, not statistically significant. Normonatraemia 37.9%, hyponatraemia 46.6%, and odds ratio (95% CI) 1.43 (0.90–2.28); $P=0.13$. The risk of death within 30 days in the mild and moderate groups increased by 46 and 27% respectively compared to normonatreamia but not statistically significant. Within 30 days – normonatremia 117/190 (61.6%), mild 36/68 (52.9%), moderate 27/48 (56.3%), and severe 0/2. Odds ratios: normonatraemia 1.00, mild 1.46 (0.83–2.55), $P=0.19$; moderate 1.27 (0.67–2.42), $P=0.46$, and severe NA.

Conclusions

Hyponatraemia is a negative prognostic indicator in lung cancer patients. Further studies are needed to see whether correction of hyponatraemia has any survival benefit.

Disclosure

The presenting author has received educational grant from Otsuka.

DOI: 10.1530/endoabs.37.EP1083

EP1084

Somatostatinoma in patient with neurofibromatosis 1 – case report

Violetta Rosiek[1], Magdalena Londzin-Olesik[1], Anna Zemczak[1] & Beata Kos-Kudla[2]

[1]Department of Endocrinology, School of Medicine with the Division of Dentistry, Medical University of Silesia, Katowice, Poland; [2]Department of Endocrinology, School of Medicine with the Division of Dentistry, Chair of Pathophysiology and Endocrinology, Medical University of Silesia, Katowice, Poland.

Introduction

We present a rare case of 49-year-old patient with neurofibromatosis type I and somatostatin-secreting pancreatic neuroendocrine neoplasm. World literature describes about 30 cases of duodenal somatostatinoma in NFI1 and 1/3 of these cases with metastases to the lymph nodes or liver.

Case report

In October 2013 patient was operated in emergency due to gastrointestinal tract obstruction. During the procedure inoperable head of pancreas tumour, closing duodenum was confirmed. Gastrojejuniostomia was performed, specimens from pancreas tumour were taken. Neoplasm tissue wasn't found in the examined specimens in the histopathological examination. In June 2014 core biopsy pancreas tumour was performed under control CT which resulted in discovering neuroendocrine neoplasm G2. Afterwards in 30th September 2014 patient was operated (using the method of Whipple's). Diagnosis well-differentiated neuroendocrine neoplasm G2, Ki-67 5% was confirmed (positive somatostatin reaction/expression in immunohistochemical test). In abdominal CT 17th December 2014 local recurrence and metastases to liver and lymph nodes have been identified. Stomachaches, weight loss and loose stools (4/day) since October 2014 were appeared. Evaluated concentrations of neuroendocrine markers (CgA, insulin, gastrin, serotonin and 5-hydroxyindoleactic acid) were in reference ranges. Determination of serum somatostatin level was impossible. Due to symptomatic and metastatic characters neuroendocrine neoplasm patient was treated with the somatostatin analogue. Clinical improvement (weight stabilization, diarrhea withdrawal) was observed.

Conclusion

Somatostatin-secreting pancreatic neuroendocrine neoplasm occurs very rarely and affects patients with neurofibromatosis type I. Somatostatin analogues in neuroendocrine neoplasm treatment resulted in great effectiveness.

DOI: 10.1530/endoabs.37.EP1084

EP1085

Insulinoma: a multicentre and retrospective analysis of the Spanish experience during three decades

Pedro Iglesias[1], Christian Lafuente[1], María Angeles Martín Almendra[2], Antonio López-Guzmán[3], José Carlos Castro[4] & Juan José Díez[1]

[1]Department of Endocrinology, Hospital Ramón y Cajal, Madrid, Spain; [2]Department of Endocrinology, Hospital Virgen de la Concha, Zamora, Spain; [3]Department of Endocrinology, Hospital Nuestra Señora de Sonsoles, Avila, Spain; [4]Department of Endocrinology, Hospital General, Segovia, Spain.

Objective

To characterise insulinoma diagnosed and treated in the period 1983–2014 in various hospitals in Spain.

Methods

Inclusion criteria were the presence of biochemical and morphological criteria compatible with insulinoma and/or histologic demonstration of tumour.

Results

Twenty-nine patients (23 women (79.3%); mean age 48.7±17.4 years (range, 16–74)) were recruited. In 26 (89.7%) cases the tumor was sporadic and the rest (3 women, 10.3%) was presented in the context of multiple endocrine neoplasia (MEN 1). There were 3 (10.3%) multiple insulinomas, one associated with MEN and 2 (6.9%) sporadic malignant insulinomas. The majority ($n=18$, 62.1%) showed fasting hypoglycaemia, about a third (31%) both postprandial and fasting hypoglycaemia and 6.9% postprandial hypoglycaemia only. Time to reach nadir of glucose (37.3±6.5 mg/dl) in the fasting test was 9.0±4.4 h, with maximal insulinaemia of 25.0±20.3 mcU/ml. Abdominal CT detected insulinoma in 75% of patients. Twenty seven (93.1%) patients underwent surgery (enucleation, 18 (66.7%) and subtotal pancreatectomy was performed in 9 (33.3%) patients; mean tumour size was, 1.7±0.7 cm). Surgery achieved cure in the majority ($n=24$, 88.9%) of patients.

Conclusion

Insulinoma is usually a benign, small and solitary tumour, affecting predominantly women aged 45–50 years which is habitually located with abdominal CT. Open surgery by enucleation is the most commonly used surgical technique achieving a high cure rate.

DOI: 10.1530/endoabs.37.EP1085

EP1086

Psoriatic patients have not an increased risk of polycystic ovary syndrome-results of a retrospective study

Gina Botnariu[1], Daniel Cioloca[1], Catalina Holban Cioloca[1], Anca Chiriac[2,3] & Alexandru Florescu[1]

[1]University of Medicine and Pharmacy 'Gr. T. Popa', Iasi, Romania; [2]Apollonia University, Iasi, Romania; [3]Nicolina Medical Center, Iasi, Romania.

Objective

There are a few studies regarding the relationship between psoriasis and polycystic ovary syndrome (PCOS).

The aim of present study was to identify the prevalence of PCOS in patients with psoriasis.

Material and methods

A retrospective study has been performed upon 1236 patients diagnosed with psoriasis (male 54.13%, female 45.87%) during 2004–2011. The prevalence of polycystic ovary syndrome (PCOS) has been quantified.

Results

Out of the 1236 patients diagnosed with psoriasis, 669 were men (54.13%) and 567 (45.87%) women, 533 women of reproductive age with psoriasis. PCOS was diagnosed in eight patients, representing 1.5% of female patients of reproductive age with psoriasis.

Conclusion

Although previous data have suggested a higher prevalence of PCOS in women with psoriasis one, our data does not support the correlation. Limitations of present study: no healthy age and body mass index (BMI)-matched controls.

DOI: 10.1530/endoabs.37.EP1086

EP1087

Case report of successfully treated congenial hyperinsulinism in Armenia

Gayane Bayburdyan & Yelena Aghajanova

Yerevan State Medical University, Yerevan, Armenia.

Introduction

Congenital hyperinsulinism is the most common cause for recurrent hypoglycaemia in neonates and infants. Uncontrolled hypoglycaemia leads to seizures and long-term cerebral damage. Herein, we report a case of congenital hyperinsulinism (persistent hyperinsulinaemic hypoglycaemia of infancy, nesidioblastosis) and review of the relevant literature regarding on the aetiology, pathogenesis, clinical and pathological features, diagnosis and treatment of this disorder.

Case report
A term male newborn with a birth weight of 2900 g, delivered vaginally without complications, presented with tonic-clonic seizures and hypoglycaemia of 0.5 mmol/l (normal range 1.7–2.8 mmol/l) on the second day of life. Intravenous infusion of 12.5% glucose solutions at a rate of 10–17 mg/kg and dexamethazone 0.8 mg/kg were given to maintain a stable blood sugar level. The plasma insulin level was 32.3 μU/ml (normal values 2.6–24.9 μU/ml) and blood sugar level was between 0.5 and 7.2 mmol/l on day 30 of his life. These results suggest nesidioblastosis, or persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI). To confirm the diagnosis, the diagnostic laparoscopy was performed. During the surgery, enlarged hyperplastic Langergance islets were visualised, patient was subjected to a pancreatectomy with resection of 50% pancreatic gland. Pathological analysis was consistent with insulinoma.
Conclusions and follow up
Congenital hyperplasia and dysplasia of pancreatic islet cells and a focal adenomatous hyperplasia was diagnosed by pathological analysis of surgical material, as well as clinical presentation. At present time, the patient is 3 years old, maintains euglycaemia with fractionated feeding and has a normal psychomotor development. This is the first case of diagnosis and successful treatment of congenital hyperinsulinism in Armenia.

DOI: 10.1530/endoabs.37.EP1087

EP1088

Hodgkin's lymphoma presented as goitre: case report

Iva Jakubikova[1,2], Jan Cap[1,2] & Filip Gabalec[1,2]
[1]4th Department of Internal Medicine, University Hospital in Hradec Kralove, Hradec Kralove, Czech Republic; [2]Charles University Faculty of Medicine in Hradec Kralove, Hradec Kralove, Czech Republic.

Introduction
Lymphomas account for <5% of thyroid malignancies. The vast majority of them are non-Hodgkin's lymphomas (NHL), especially mucosa-associated lymphoid tissue lymphomas (MALT) and diffuse large B-cell lymphomas (DLBCL). However, Hodgkin's lymphoma affecting thyroid gland is very rare. Worldwide has been reported <50 cases so far and we describe another one.
Case report
A 22-year-old woman was referred to our department of endocrinology for a rapid enlargement of thyroid gland. Prior short therapy of corticosteroids soothed the growth, but after its cessation the goitre enlarged causing dysphagia, dry cough and stridor. The patient also suffered with night sweats and intermittent fever. Both physical and ultrasound examination found unilaterally large hypoechoic right thyroid lobe, deviating trachea to the left and at least two suspicious supraclavicular lymph nodes along the right sternocleidomastoid muscle. According to laboratory the patient was euthyroid, thyroid antibodies were negative, no significant changes in blood count. Elevated was lactate dehydrogenase (LDH 6 μkat/l), C-reactive protein (CRP 53 mg/l), erythrocyte sedimentation rate (ESR 76 mm/first hour). The fine-needle aspiration cytology (FNAC) was highly suspicious of lymphoma, but the flow cytometry did not prove any abnormal population of lymphocytes consistent with non-Hodgkin's lymphoma. Therefore a diagnostic excision from the right thyroid lobe was performed. Final diagnosis of classical Hodgkin's lymphoma, nodular sclerosing subtype was established. The department of haematology classified our patient for advanced stage IIB + E (extranodal involvement). The patient was treated with six cycles of eBEACOPP chemotherapy, reaching total remission according to PET/CT scan, further radiotherapy was not indicated.
Conclusion
Hodgkin's lymphoma of thyroid is rare, rapid growth can mimic primary thyroid carcinoma, FNAC can mimic thyroiditis, lacking diagnostic Reed-Sternberg cells. Flow-cytometry is not helpful in Hodgkin's disease. A biopsy is usually necessary to confirm the right diagnosis.

DOI: 10.1530/endoabs.37.EP1088

EP1089

To be or not to be a primary hepatic neuroendocrine tumour

Ioana Maria Lambrescu[1,2], Sorina Martin[1,3], Cristina Blaga[3], Luminita Cima[1,2] & Simona Fica[1,3]
[1]Endocrinology Department, Carol Davila University of Medicine and Pharmacy, Eroii Sanitari Avenue 8, 050474, Bucharest, Romania; [2]PhD Student in the Project, Sectorial Operational Programme Human Resources Development (SOPHRD) Contract Number POSDRU/159/1.5/S/141531, Bucharest, Romania; [3]Endocrinology Department, Elias Hospital, Marasti Avenue 17, 011461, Bucharest, Romania.

Introduction
Primary hepatic neuroendocrine tumours (PHNTs) are a very rare medical entity. Usually, the liver represents the preferential site for metastasis. Large sized, singular nodules are the usual presentation of PHNTs. We report a patient with PHNTs at 4 years of tumour free follow-up.
Case presentation
A 45-year-old Caucasian female who presented with nausea, vomiting, diarrhoea, accompanied by diffuse abdominal pain, was found to have on contrast enhanced computer tomography an encapsulated liver mass measuring 7/8.5/9 cm, which contained multiple daughter cysts separated by a matrix. In this context, the initial diagnosis was of an Echinococcus cyst. The patient underwent an uneventful left atypical hepatic resection. The resected specimen displayed a centrally brown–greyish solid cystic tumour measuring 8 cm, outlining a heavily vascularized cell proliferation with trabecular and band disposition and a homogenous growth pattern. The result of the immunohistochemical stain was diffusely positive in the tumour cells for chromogranin, synaptophysin and neuron specific enolase with 2–4% nuclear reactivity for Ki-67 index. Postoperatory, the specific neuroendocrine markers (serum Chromogranin A and 24-h-urinary 5-hydroxyindolacetic acid) were within the normal range. The patient underwent In^{111} DTPA-octreotid scan, that showed no regions that were somatostatin receptor positive, and the PET scan with 5HTP could not find any suspicious lesions. The patient is now at 4 years of follow-up with no local recurrence or distant metastasis.
Conclusions
We report a case of primary PHNT in an adult female presenting with abdominal pain and diarrhoea, at 4 years of follow up with no signs of recurrence. We think that PHNT is an over-diagnosed medical entity, as most cases in English literature are incompletely documented, which makes it hard to establish the exact percentage of this type of tumour. In order to exclude an occult primary neuroendocrine tumour, thorough long-term investigations are required.

DOI: 10.1530/endoabs.37.EP1089

EP1090

Benign and malignant thyroid disease in patients with acromegaly

Irina Tenu[2], Antonia Kiraly[2], Ileana Duncea[1,2], Ana Valea[1,2], Alina Silaghi[2] & Cristina Ghervan[1,2]
[1]Department of Endocrinology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania; [2]Endocrinology Clinic, Cluj County Clinic Emergency Hospital, Cluj-Napoca, Romania.

Introduction and purpose
Acromegaly is characterised by a chronic increase of GH and IGF-1 levels that may induce various clinical symptoms and multisystem comorbidities. The purpose of this study is to evaluate the type and frequency of thyroid disease most often associated with acromegaly patients.
Material and methods
We conducted a retrospective observational study analysing the data from the observation charts of 77 patients with acromegaly (58 females and 19 males), with a mean age of 54 years, evaluated between July 2007 and July 2014 in the Endocrinology department. The recorded data were: acromegaly status, sonographic thyroid morphology, thyroid function, and pathological data after surgical cure. The statistical analysis was conducted using Microsoft Excel 2010.
Results
The acromegaly status was active for 49% of the patients, controlled in 37%, and cured in 14%. 96% of the patients were treated, the most common combination being surgical treatment + radiotherapy + medication (39%). Thyroid disease was diagnosed in 54 patients (70.12%). Nodular goiter had the highest prevalence rate (27.27%), followed by Hashimoto's thyroiditis (12.98%) and thyroid cancer (10.38%). The occurrence of thyroid pathology was almost equal in women (70.68%) and men (68.42%). Thyroid disease was most frequent for the ≥60 years old age range, while acromegaly was most frequent in the 40–50 years old range. Other malignant diseases were diagnosed in 5% of the patients.
Conclusions
Thyroid disease is a frequent complication of acromegaly, with nodular goiter having the highest prevalence rate. In terms of malignant pathology, in our study, thyroid cancer had the highest prevalence rate (10.38%). This indicates the need for a systematic evaluation in order to achieve an early diagnosis.

DOI: 10.1530/endoabs.37.EP1090

EP1091

Mutation in CDKN1B 3′-UTR region in a patient with acromegaly and primary hyperparathyroidism

Elizaveta Mamedova, Natalia Mokrysheva, Ekaterina Pigarova, Elena Przhiyalkovskaya, Evgeniy Vasiliev, Lyudmila Rozhinskaya & Anatoliy Tiulpakov
Endocrinology Research Center, Moscow, Russia.

Introduction
Multiple endocrine neoplasia type 4 (MEN4) is a rare disorder, caused by inactivating mutations in *CDKN1B* gene that encodes $p27^{kip1}$ cyclin-dependent kinase inhibitor. To date nine different germline *CDKN1B* mutations have been described in patients with clinical features of multiple endocrine neoplasia type 1 (MEN1) negative for *MEN1* mutations (MEN1 phenocopies).
Case report
We present a female 54 y.o. with clinical features of MEN1: active acromegaly due to GH-producing pituitary macroadenoma after two consecutive neurosurgical interventions (transcranial and transsphenoidal) with remaining tissue in left cavernous sinus, requiring treatment with long-acting somatostatin analogues; mild primary hyperparathyroidism with ultrasound signs of superior right parathyroid adenoma; multinodular colloid goiter; extirpation of uterus and ovaries for adenomatous endometrial polyp, multinodular fibromyoma and endometrioid cyst; right mammary gland resection for benign lesion. Genetic testing for *MEN1* germline mutation was negative. Genomic DNA from a blood sample of this patient together with ten other MEN1 phenocopies underwent high-throughput sequencing on the Ion Torrent Personal Genome Machine (Life Technologies) using a custom-designed AmpliSeq panel for the sequencing of a variety of genes, including *CDKN1B*, which could be responsible for the development of MEN1 phenocopies. We revealed a heterozygous mutation in 3′-UTR g.3897G>T (c×8G>T) in *CDKN1B* gene, which was *in silico* tested with free web-based application for disease-causing potential of DNA sequence alterations MutationTaster, detecting splice site alterations. Further *in vitro* studies are needed to confirm, whether this mutation alters protein function.
Conclusions
To our knowledge, we describe the first mutation in 3′-UTR of *CDKN1B* in a patient with MEN1 phenocopy.
Disclosure
This work was supported by the Grant of the President of the Russian Federation for young PhD scientists (awarded to E G Przyjalkowski : grant Number: MK-5411.2014.7).

DOI: 10.1530/endoabs.37.EP1091

EP1092

Analysis of current indications to bilateral adrenalectomy

Maria Kurowska, Joanna Malicka, Agnieszka Zwolak & Jerzy S Tarach
Department of Endocrinology, Medical University, Lublin, Poland.

Introduction
Bilateral adrenalectomy (BA) is rarely applied as a therapeutic procedure. It serves as a life-saving treatment in patients with persistent Cushing's disease after an ineffective pituitary surgery or in ectopic ACTH production. Other indications for BA are: bilateral adrenocortical adenomas, congenital adrenal hyperplasia and bilateral phaeochromocytoma in patients with hereditary paraganglioma-phaeochromocytoma (PPS/PGL) syndromes. It is also a procedure of choice in bilateral adrenal metastases. The aim of the study was to determine the indications to BA in patients hospitalized in our ward between 2001 and 2012.
Material and methods
12 patients (7F; 5M) aged 19–72 years. Studies were based on retrospective analysis of medical records.
Results
Patients were divided into three groups. Group 1:7 patients (4F; 3M) with bilateral phaeochromocytoma (MEN2 syndrome – four patients, PPS/PGL-1 patient, von Hippel – Linadu – one patient, one woman with sporadic bilateral phaeochromocytoma). Among three patients from group 2 the indications to BA were adrenal metastases of renal clear cell carcinoma in two and a metastasis to one adrenal gland coexisting with adenoma of the other in one case. Group 3: two women with Cushing's disease. One of them was operated 31 years earlier propter corticotroph microadenoma and the second – because of atypical pituitary macroadenoma refractory to radiation, neurosurgical and pharmacological treatment. Patients with congenital disorders (six), Cushing's disease (two) and one with metastasis and adenoma, underwent synchronous bilateral or two-stage adrenal surgery. Female with sporadic bilateral phaeochromocytoma was operated twice at interval of 10 years and two patients with adrenal metastases at intervals of 3–4 years. Two patients died after a year and 3 years due to the progression of the underlying disease. The remaining are still alive (from 2 to 31 years after surgery).
Conclusions
Currently, the prevalent indication to BA is bilateral phaeochromocytoma, mostly in the course of underlying hereditary neoplasmatic syndrome.

DOI: 10.1530/endoabs.37.EP1092

EP1093

Audit of adrenal tumours at Vilnius University Hospital Santariskiu Klinikos (VUHSK): 4 year results

Zydrune Visockiene[1,2] & Milda Girdziute[2]
[1]Vilnius University, Vilnius, Lithuania; [2]Vilnius University Hospital Santariskiu Klinikos, Vilnius, Lithuania.

The aim of study was to make a retrospective audit of diagnostic approach of symptomatic and asymptomatic patients with adrenal tumours diagnosed at VUHSK from 2010 to 2013.
Methods
Cases coded as D35.0; D44.1; E27.0; E27.5; E27.8; E27.9 according to ICD-10 classification were retrieved from database. Electronic data capture system was used to collect information.
Results
There were 527 (123 men, 404 women) patients, age 62.5±11 years, diagnosed with adrenal tumours from 2010 to 2013: 281 patient had symptoms: hypertension – 91.1%, episodic elevations of blood pressure – 34.5%, hypokalaemia – 18.1%, 246 patients had no symptoms. There were 71.5 and 94.7% of tumours found incidentally in symptomatic and asymptomatic groups respectively. Suspicion of hormonal hypersecretion and proper diagnostic approach was used only in 80 (28.5%) of symptomatic patients. Symptomatic patients were assessed for hormonal activity as compared to asymptomatic: aldosterone – 64.8 vs 43.9%, renin – 54.4 vs 30.1%, metanephrine/normetanephrine or adrenaline/noradrenaline – 61.2 vs 22.0% ($P<0.001$ for all), cortisol – 39.2% in both groups, comprehensive analysis – 14.6 vs 6.5% ($P=0.003$). Computed tomography confirmed diagnosis in 93% of cases in both groups; with larger tumors in asymptomatic compared to symptomatic patients (24.7±14.0 vs 22.5±14.4 mm, $P=0.02$).
Non-secreting tumours were diagnosed in 81.4 vs 94.8%, aldosteroma – in 10.3% vs 1.2%, phaeochromocytoma – in 6.8 vs 0.8% ($P<0.001$ for all), carcinoma – in 1.1 vs 0.4%, $P=0.378$ comparing symptomatic and asymptomatic groups respectively. There were 45% of secreting tumours in symptomatic patients for whom proper diagnostic approach was used based on symptoms.
Conclusions
The proportion of patients having adrenal tumours with and without symptoms is similar. Although hormonal assessment should be performed in all patients, clinical symptoms should urge the doctor for comprehensive assessment as the prevalence of secreting tumours is the highest in symptomatic patients for whom proper diagnostic approach was used to clarify the diagnosis.

DOI: 10.1530/endoabs.37.EP1093

EP1094

Plasma chromogranin A and chromogranin B concentrations in untreated patients with mid gut carcinoid and their biochemical response to octreotide

Lee Armstrong, Teresa Rea, Brian Johnston & David McCance
Belfast HSCT, Belfast, UK.

We measured chromogranin A (CgA) and chromogranin B (CgB) in 36 patients, recently confirmed to have a midgut carcinoid tumour (MGC), prior to the commencement of octreotide treatment. Blood samples were taken before and after a bolus injection of 50 μg octreotide. There were 21 males, 15 females, age range 28–76 median 61 years.
Basal CgA, expressed as times the upper limit of normal (ULN) ranged from 333.3 to 0.5 ULN. Basal CgB ranged from 33.7 ULN to zero (undetectable). Of 36 patients, 21 had highly elevated basal CGA (> X5 ULN), ten had moderately elevated CGA (X2–X5 ULN) and five patients had normal or marginally raised

CgA. Nine patients had CgB > X2 ULN, four patients had elevated CgB up to X2 ULN and 23 had normal CGB. All patients with elevated CgB also had raised CgA. Fourteen of 29 patients with raised basal CgA showed a significant (>20%) decrease in CgA 60 min after octreotide injection. Three showed an increase of >20%. The remaining patients showed no significant change. Seven of 11 patients with a high basal CgB showed a decrease >20% 60 min post injection. It is generally observed that very high CgA concentrations before treatment begins may indicate advanced stage of disease and therefore poor prognosis. A lack of response may also predict a poor prognosis. However, good biochemical response to bolus octreotide may indicate a good future response to treatment. CgB was performed to assess its usefulness as a supplementary diagnostic test in neuroendocrine tumour patients with normal CgA. We did not observe any patients with raised CgB only according to the supplied kit reference range.

DOI: 10.1530/endoabs.37.EP1094

EP1095

Endoscopic ultrasound features of familial vs sporadic pancreatic neuroendocrine tumours: a single-centre retrospective study

Gianluca Tamagno[1], Vanessa Scherer[1], Alberto Caimo[2], Simona R Bergmann[1] & Peter H Kann[1]
[1]Division of Endocrinology and Diabetology, University Hospital – Philipp's University, Marburg, Germany; [2]Faculty of Economics, University of Lugano, Lugano, Switzerland.

Introduction
Pancreatic neuroendocrine tumours (pNETs) can either occur in patients with a familial syndrome, like multiple endocrine neoplasia type 1 (MEN-1), or being sporadic. In the last decade, endoscopic ultrasound (EUS) has become one of the first-line investigations for the characterisation of pNETs. The ultrasonographic features of a pNET might differ depending on the familial vs sporadic pathogenesis of the tumour. Therefore, the EUS findings might help and direct the accurate definition of a pNET with a possible impact on the most appropriate diagnostic and therapeutic management of pNET patients.
Patients and methods
In this single-centre retrospective study, we have reviewed the EUS characteristics of 131 pNETs from 38 MEN-1 patients and 14 pNETs from 13 sporadic disease patients at the time of their first EUS assessment. The patients attended consecutively our institution over a 5-year-time period. With the goal of defining the EUS features of MEN-1 vs sporadic pNETs, we have analysed the most relevant morphological and ultrasonographic aspects of the tumours and compared the findings between the two patient groups.
Results
Patients with MEN-1 are more likely to present with multiple (3.4 vs 1.1 tumours/patient) and bigger (21.6 vs 7.5 mm) pNETs in comparison to those with sporadic disease. There is no statistical difference with regard to morphology, definition of the margins, and vascularization of the pNETs between the two groups. However, pNETs appear to be significantly more heterogeneous in patients with MEN-1 than in those with sporadic disease.
Conclusion
In patients with MEN-1 pNETs tend to be more numerous, bigger, and more heterogeneous than in patients with sporadic disease. EUS can help with the precise characterization of a pNET, including the definition of ultrasonographic features which can distinguish a familial vs sporadic disease.

DOI: 10.1530/endoabs.37.EP1095

EP1096

Thyroid carcinoma in relation to gender and age in patient who were treated with total thyroidectomy for different thyroid disorders

Entela Puca[1], Kadir Burak Koza[1], Emiljana Huti[1], Sonila Bitri[1], Edmond Puca[2] & Agron Ylli[2]
[1]American Hospital 2, Tirana, Albania; [2]UHC Mother Teresa, Tirana, Albania.

Aim of the study
Thyroid cancer comprises the most common endocrine malignancy and a variety of studies have examined the incidence of carcinomas in n thyroid disorders. Objective of the present retrospective study was the assessment of the possible influence of age and gender parameters in the presence of thyroid carcinoma in a patient who underwent total thyroidectomy.
Material and methods
We studied 107 patients (96 females/11 males) underwent total thyroidectomy because of nodular goitre in our Department. The classification of patients in both genders was conducted in the following age-groups: a = 16–39 years, b = 40–59 years, c = > 60 years. Thyroid specimens were histopathologically examined at our Pathology Department for the establishment of the final diagnosis of benignity or malignancy. Thyroid cancer cases were categorized in relation to gender and age group.
Results
40 patients (37.3%) were diagnosed with carcinoma (rate females:males 9:1), while 67 patients (62.7%) were free of malignancy. The incidence of thyroid cancer in male subjects was 36.5% (4/11). The respective cancer frequency in female subjects was 37.5 0% (36/96). The incidence of carcinoma per age group was in males: a = 3/4;75%, b = 0 and c = 1/5; 20%. In females it was respectively: a = 13/27; 48.1%, b = 20/51; 39.2%, c = 3/18; 16.62%.
Conclusions
We found the highest prevalence of thyroid carcinomas among the females. Age-specific rates of thyroid carcinoma were higher among women than men across all age groups. In males groups there was a high incidence in the age group 20–39 years and >60 years. Total thyroidectomy appears to be the therapeutic method of choice in men with indication of surgical removement of a goitre which belong to the above age groups. Contrarily, there was a high incidence in women age group 15–39 with a pick 40–59 years.

DOI: 10.1530/endoabs.37.EP1096

EP1097

The sensitising action of a TIM16 inhibitor towards chemotherapeutic agents in human breast cancer cells depends on TIM16 expression

Teresa Gagliano[1], Federico Tagliati[1], Eleonora Riva[1], Denise Zerbini[1], Silvia Sambugaro[1], Erica Gentilin[1], Simona Falletta[1], Katiuscia Benfini[1], Carmelina Di Pasquale[1], Claudio Trapella[2], Severo Salvadori[2], Ettore degli Uberti[1] & Maria Chiara Zatelli[1]
[1]Section of Endocrinology, Department of Medical Sciences, University of Ferrara, Ferrara, Italy; [2]Department of Chemical and Pharmaceutical Sciences, Univeristy of Ferrara, Ferrara, Italy.

TIM16 a component of the translocase complex TIM23 of the mitochondrial inner membrane is encoded by the Magmas gene. Magmas was found to be over-expressed in human pituitary adenomas. Silencing Magmas in ACTH secreting rat pituitary adenoma cells enhances sensitivity to pro-apoptotic stimuli. Moreover, Magmas overexpression protects GH secreting rat pituitary adenoma cell lines towards apoptosis. Recently, we found that compound 5, a TIM16 inhibitor, is not cytotoxic but enhances the proapoptotic effects of staurosporine by reducing mitochondrial membrane potential (MMP) activation in a medullary thyroid carcinoma cell line, suggesting that compound 5 may be useful for cancer treatment in association with chemotherapeutic drugs. Since breast cancer (BC) displays high chemoresistance, the aim of our study was to investigate Magmas expression in human breast cancer cell lines and to verify whether compound 5 could increase the effects of a chemotherapeutic agent, such as Doxorubicin in these cells. As an *in-vitro* model we used three human breast cell lines: MCF7 and MDA-MB231 carcinoma cell lines and MCF12A normal breast cell line. We found that Magmas protein is highly expressed in the MCF7 cell line as compared to MDA-MB231 and MCF12A cells.
Our data show that treatment with compound 5 did not influences cell viability in the three cell lines, while Doxorubicin decreases this parameter by 20–30%. Only in MCF7 cells co-treatment with compound 5 enhances by 15–20% the antiproliferative effects of Doxorubicin, measured as cell viability and BrDU incorporation. MitoTox Glo assay shows that in MCF7 cells the enhancing effects of compound 5 on Doxorubicin action are due to mitochondrial toxicity. In summary, these data suggest a role for the use of compound 5 as a sensitising agent for chemoresistant breast cancer expressing high levels of TIM16.

DOI: 10.1530/endoabs.37.EP1097

EP1098

Differential gene expression between primary and secondary hyperparathyroidism

Shih-Ping Cheng, Chien-Liang Liu, Jie-Jen Lee, Han-Hsiang Chen & Chih-Jen Wu
MacKay Memorial Hospital and Mackay Medical College, Taipei, Taiwan.

The pathophysiology differs significantly between primary and secondary hyperparathyroidism. Whole exome sequence analysis of parathyroid adenomas showed few somatic variants. The underling mechanisms of the occurrence of sporadic primary hyperparathyroidism remain largely unknown. In this study, we analysed the differences in gene expression between primary and secondary hyperparathyroidism to explore potential functional alterations. Total RNA was extracted from tissues obtained during parathyroidectomy. Gene expression microarray and bioinformatic pathway analysis were performed. Parathyroid tissues were classified in an unsupervised manner into primary and secondary clusters. Parathyroid adenomas showed higher expression of cell adhesion molecules. On the contrary, secondary hyperparathyroidism exhibited upregulation of complement/coagulation cascades and mTOR signalling pathway. In conclusion, our study demonstrates that different pathophysiology led to differential gene profiling in hyperparathyroidism. The results from pathway analysis may have diagnostic and therapeutic implications.

Disclosure
This work was supported by the Ministry of Science and Technology of Taiwan (MOST 103-2314-B-195-015-MY3).

DOI: 10.1530/endoabs.37.EP1098

EP1099

Surgical correlation of thyroid nodules categorised as potential follicular neoplasms in core-needle biopsy (CNB)

Miguel Paja[1], Rosa Zabala[2], Igone Corta[2], Amaia Expósito[4], Laura Calles[1], Aitzol Lizarraga[1] & Aitziber Ugalde[3]
[1]Endocrinology Department, Hospital Universitario de Basurto, Bilbao, Basque Country, Spain; [2]Radiology Department, Hospital Universitario de Basurto, Bilbao, Basque Country, Spain; [3]Pathology Department, Hospital Universitario de Basurto, Bilbao, Basque Country, Spain; [4]Endocrine Surgery Department, Hospital Universitario de Basurto, Bilbao, Basque Country, Spain.

In our centre we use CNB for routine study of thyroid nodules since 2005. Four diagnostic categories for CNB's results have been standardised: insufficient; benign; follicular proliferation (FOL), including follicular and oncocytic neoplasms; and malignant. Diagnosis of FOL was defined according to the presence of microfollicular patterned biopsies with scant or absent colloid, sometimes with minimal pleomorphism or discrete nuclear changes. This category could be equivalent to AUS/FLUS and FN/SFN, III and IV categories in BSRTC, encompassing undetermined diagnosis leading to surgical evaluation. We review surgical results in operated patients. A series of 166 patients (33 men), mean age, 52.8 years (SD 14.5) from 3750 CNBs (207 FOL; 5.5%) all of whom underwent surgery, from October 2005 to December 2014 were retrospectively analysed. They included 102 diagnosed as pure follicular lesions and 64 as oncocytic FOL. The false-positive rate, unnecessary surgery rate, and malignancy rate for the CNB patients according to the final diagnosis following surgery were evaluated. In surgical specimens 32 patients (19.3%) had non-neoplasms (unnecessary surgery), all of which were nodular adenomatous hyperplasia. The remaining 134 nodules were true neoplasms, 31 (18.7%) malignant. Malignant included 16 follicullar carcinomas, 13 papillary carcinomas. one medullary carcinoma and one poor-differentiated thyroid carcinoma. In 23 cases there were incidentally discovered papillary carcinomas (1–12 mm of size) in the same or contralateral lobe of the biopsied lesion. From 102 adenomas, 17 carried an incidental PTC (16.7%). Globally, there were 54 carcinomas with a CB of FOL (32.5%). CNB shows good/fine precision in diagnosing follicular neoplasms, but as FNA, fail to distinguish adenomas from carcinomas, with a malignancy rate around 20%. We remark the frequent association of benign neoplasm (adenomas) with malignant lesions in the same thyroid (16.7%), supporting surgical treatment when this CB diagnosis is obtained.

DOI: 10.1530/endoabs.37.EP1099

EP1100

Emotional state in men and women with acromegaly after pituitary adenomas

Lina Lasaite[1], Robertas Knispelis[2], Jurate Lasiene[2] & Lina Barsiene[2]
[1]Institute of Endocrinology, Lithuanian University of Health Sciences, Kaunas, Lithuania; [2]Clinic of Endocrinology, Clinical Hospital of Lithuanian University of Health Sciences, Kaunas, Lithuania.

Adult patients with acromegaly after pituitary adenomas usually have emotional problems, impaired quality of life. Objective was to detect possible differences of emotional state between patients with acromegaly after pituitary adenomas and healthy age- and sex-matched controls and to outline possible gender-specific differences.

Patients and methods

12 males (age 49.6±10.2 years) and 29 females (age 51.5±9.5 years) with acromegaly after pituitary adenomas; 12 control males (age 44.7±14.6 years) and 29 control females (age 50.4±12.7 years). Average duration since diagnosis of acromegaly was 7.1±8.9 years. Emotional state (domains of tension-anxiety, depression-dejection, anger-hostility, vigour-activity, fatigue-inertia, confusion-bewilderment) was evaluated using Profile of Mood States (POMS).

Results

Anger-hostility was significantly lower in men with acromegaly than in control men (9.5±5.0 vs 14.8±7.5, $P=0.039$). In women with acromegaly tension-anxiety (9.3±5.9 vs 4.5±6.0, $P=0.005$) was significantly higher than in control women. No significant differences in emotional state was detected betweeen men and women with acromegaly and between men and women in the control group, only some statistical trends. In acromegalic patients there was statistical trend for men to have higher vigour activity (16.8±4.8 vs 13.8±5.2, $P=0.060$) than women; in age- and sex-matched controls there was statistical trend for men to have higher anger-hostility (14.8±7.5 vs 9.7±5.7, $P=0.061$) than women.

Conclusion

Men with acromegaly after pituitary adenomas have lower anger-hostility level and women with acromegaly after pituitary adenomas have higher tension-anxiety level than age- and sex-matched controls.

DOI: 10.1530/endoabs.37.EP1100

EP1101

Von Hippel–Lindau disease: report of two cases

Anna Dabrowska[1], Jerzy Tarach[1] & Agnieszka Zwolak[1,2]
[1]Chair and Department of Endocrinology, Medical University of Lublin, Poland, Lublin, Poland; [2]Chair of Internal Medicine and Department of Internal Medicine in Nursing, Medical University of Lublin, Poland, Lublin, Poland.

Introduction

Von Hippel–Lindau (VHL) disease is a rare autosomal dominant syndrome (1/36 000 live births) with highly penetrance that predisposes to the development of benign and malignant, highly vascularised tumours in many organs.

Case reports

Two women with VHL, without family history of VHL, were admitted to Department of Endocrinology for checkups. The diagnosis was made based on genetic tests.

Patient A

A 53-year-old woman, after partial right adrenalectomy in 1976 and total left adrenalectomy in 1979 due to bilateral pheochromocytoma. At present, she has no hypertension and typical symptoms of adrenal insufficiency. Hormonal tests revealed normal concentrations of serum cortisol and 24 h urinary cortisol in the presence of elevated serum ACTH that may indicate low adrenal reserve. The administration of hydrocortisone (10–20 mg/day) was recommended, in case of stress. The levels of serum chromogranin-A, dopamine and noradrenaline as well as 24 h urinary methoxycatecholamines were in normal range. All body scintigraphy and abdomen CT scan did not show phaeochromocytoma recurrence.

Patient B

A 44-year-old woman, with right retina haemangioblastoma leading to blindness, after resection of cerebellum haemangioblastoma (with right hemiparesis and imbalances) and clear-cell carcinoma of the left kidney, with renal cysts. At present, she has no hypertension. Hormonal tests revealed normal concentrations of serum ACTH and cortisol and 24 h urinary cortisol as well as serum chromogranin-A, dopamine, noradrenaline, urinary 5-HIAA. Abdomen CT scan showed hepatic vascular malformations and two pancreatic tumours. In head MRI

scan, the lesions: in right frontal lobe and in right eyeball were found. Somatostatin receptor scintigraphy confirmed increased radioisotope accumulation in pancreas and in right orbit. We excluded phaeochromocytoma. The diagnosis of pancreatic NETs, without hormonal activity, was made and the surgery is considered. Moreover, stereotactic radiotherapy for brain lesion was recommended.
Conclusions
Some manifestations of VHL cause that endocrine care is needed to optimize patients' treatment.

DOI: 10.1530/endoabs.37.EP1101

EP1102

Enucleation of pancreatic proinsulinoma: case report

Ana Pires Gonçalves[1], Rui Almeida[2], Hercilia Martins[3], Madalena Lourenço[4], Jorge Pereira[5], Bruno Peixe[6], Ana Rita Clara[2], Conceição Viegas[2], Ana Marta Nobre[7], Sílvia Silva[7], Jorge Paulino Pereira[7] & Mário Lazaro[2]
[1]Internal Medicine Service – Endocrinology's Division – CHAlgarve, Faro, Portugal; [2]Internal Medicine Service – CHAlgarve, Faro, Portugal; [3]Clinical Pathology Service – CHAlgarve, Faro, Portugal; [4]Day Hospital Nurse – CHAlgarve, Faro, Portugal; [5]Radiology Service – CHAlgarve, Faro, Portugal; [6]Gastroenterology Service – CHAlgarve, Faro, Portugal; [7]Hepato-pancreato-biliary Surgery Division – Hospital Curry Cabral, Faro, Portugal.

Introduction
Functional islet β-cell tumours represent 1–2% of all pancreatic neoplasms. Diagnosing this type of tumour is often challenging because they present with unspecific clinical features overlapping more common syndromes. Diagnosis involves expensive testing, so, establishing whipple's triad and excluding causes of exogenous hyperinsulinaemia is crucial before initiating investigation.
Objective
To report a rare case of a proinsulinoma.
Case report
A 47-year-old woman was sent to the endocrinology department for evaluation of suspected spontaneous hypoglycaemia. There were no relevant antecedents. For 2 years she had had adrenergic/neuroglicopenic symptoms that relieved after ingestion of carbohydrate. She had gained 20 kg/2 years. Fractionated-diet, excluding simple carbohydrates, failed to improve symptoms. The patient was taught how to use a glucose meter to measure capillary blood glucose (BMT) and instructed to do a diary, that include meals content and BMT during symptoms. Study revealed hypoglycaemias (BMT (50 mg/dl) without a predictable pattern. Laboratorial investigation confirmed endogenous hyperinsulinism secondary to autonomous proinsulin secretion. A study with CTscan-with-contrast, ultrasound and ecoendoscopy, showed a single oval nodule with 17×13 mm. Given the nodule to be unique and with very suggestive features of proinsulinoma, it was decided not to perform aspiration cytology. The patient started treatment with diazoxide while waiting for surgery. In September of 2014, she underwent a tumour enucleation, without complications. The histopathological study confirmed a low-grade neuroendocrine tumour. In the postoperative period symptoms/hypoglycaemia resolved and there was no hyperglycaemia or diabetes mellitus.
Conclusion
The work-up of fasting hypoglycaemia is crucial because a wrong diagnosis can lead to unnecessary pancreatectomy or a missed pancreatic tumour. Localisation is challenging so imaging studies should only take place once the diagnosis has been established. Highly specific serum insulin assay can difficult the diagnosis. An enucleative approach minimises the risk of developing post-operative diabetes, leading to a favourable prognosis.

DOI: 10.1530/endoabs.37.EP1102

EP1103

Morphological features and functional activity of parathyroid adenomas

Yuri Aleksandrov, Dmitryi Oralov & Sergey Pamputis
Yaroslavl Medical University, Yaroslavl, Russia.

Study for morphological and hormonal changes in the parathyroid glands in 35 patients with primary hyperparathyroidism was carried out. Post-mortem material (five bodies) used to control. All patients had primary hyperparathyroidism and elevated levels of parathyroid hormone and ionized calcium in serum. Morphometric study evaluated the cellular structure (chief and oxyphil cells) and calculated the ratio of the basic elements of parathyroid cells (nucleus, cytoplasm) and stroma (collagen fibres, blood vessels). The correlation between hormonal and morphological parameters calculated using the methods of variation statistics. Levels of PTH had significant variation range from 96 to 2665 pg/ml ($X=734$, 6 pg/ml), as well as the volume of parathyroid adenomas – from 0.3 up to 31.5 cm 3 ($X=5.1$ cm^3). A direct relationship is between the level of PTH and a relative density of nuclear component parenchyma ($r=0.56$; $P=0.009$). A feedback is between PTH and a relative density of parathyroid cells cytoplasm ($r=-0.56$; $P=0.012$). There is no correlation between the level of PTH and the average number of cellular elements in the field of view ($r=0.27$; $P=0.26$). In parathyroid adenomas smaller than 1 cm^3 of correlation between levels of PTH and the increase in the size of the tumour is not ($r=0.25$; $P=0.47$). In parathyroid adenomas larger than 1 cm^3 PTH level increases with tumour volume ($r=0.55$; $P=0.01$). There is no direct correlation between level of PTH and specific morphological changes in the parathyroid glands. Secretion of parathyroid hormone depends on the intracellular and the structural changes in parathyroid adenomas. Significantly changes are correlate with the size of the tumour.

DOI: 10.1530/endoabs.37.EP1103

EP1104

Adult-onset nesidioblastosis causing hyperinsulinaemic hypoglycaemia: diagnosis and treatment challenge: a case report

Daniel-Tudor Cosma[1], Alina Silaghi[2,4], Nicolae Rednic[3,4], Sorin Barbu[3,4], Carmen Georgescu[2,4] & Ioan Andrei Veresiu[1,4]
[1]Diabetes, Nutrition and Metabolic Diseases Clinical Center, Cluj-Napoca, Cluj, Romania; [2]Endocrinology Clinic, Cluj-Napoca, Cluj, Romania; [3]Railways Clinical Hospital, Cluj-Napoca, Cluj, Romania; [4]Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Cluj, Romania.

Nesidioblastosis is defined as a diffuse proliferation of primitive pancreatic islet cells budding from ductal epithelium. This condition can cause hypoglycaemia in infants as a result of mutations in the sulfonylurea receptor or in the anatomically linked potassium channel. In adults, this disease occurs independently from these genetic mutations.
Case report
A 41-year-old male was referred to our center via emergency room with suspicion of an insulinoma after an episode of loss of consciousness with a glycemia (G) of 24 mg/dl. Further questioning revealed three similar episodes in 2012. At admission: altered general status with retrograde amnesia, dry skin and mucous membrane and deep tenderness in the epigastrum, pulse 65 b/min. The 72 h fast was stopped for symptomatic hypoglycaemia with high insulinaemia. Imaging studies were normal excepting endoscopic ultrasound which revealed a pseudolobular aspect in the pancreas tail and body. The patient was guided to a surgical clinic with dietetic recommendation and phenytoin 200 mg/day for insulinoma localization and surgical treatment. His was admitted into the surgical clinic after 3 weeks from the previous hospitalization with only two moderate hypoglycaemic episode under phenytoin treatment. The short octreotide test was interrupted due to symptomatic hypoglycaemia confirming the lack of tumour somatostatinoma receptors. Exploratory laparotomy was performed with intraoperative ultrasonography which exhibited two tumors in the pancreas tail and body. A subtotal spleno-pancreatectomy was performed. Microscopic view was consistent with nesidioblastosis and no tumour was found. The patient remains euglycaemic 10 months post-operatively.
Discussions
Nesidioblastosis is a rare cause of adult hypoglycaemia. Pre-operative differentiation from insulinoma is difficult, but mandatory when imaging studies are negative. New diagnostic tools like ^{18}F-DOPA PET scan or selective arterial calcium stimulation with hepatic venous sampling (unavailable in our country) could help establishing the diagnosis.

DOI: 10.1530/endoabs.37.EP1104

EP1105

Pituitary apoplexy

Dhiaeddine Bellarbi, Said Azzoug, Leyla Rabehi, Brahim Terki & Farida Chentli
Endocrinology and Metabolic diseases department Bab El Oued hospital, Algiers, Algeria.

Introduction
Pituitary apoplexy is a rare endocrine emergency characterized by the sudden onset of severe headaches, vomiting, visual abnormalities and pituitary dysfunction secondary to an acute hemorrhage or infarction within a pituitary adenoma.
Subjects and methods
We report a retrospective study from 2000 to 2014 of 23 cases with pituitary apoplexy. Their mean age was 38.7±14.8 years, with a male to female ratio of 2:1.
Results
Apoplexy revealed an unknown adenoma in 74%. 48% were prolactinomas, 22% were GH-secreting adenomas and 30% were non functioning adenomas. The commonest presenting symptoms were frontal and retro-orbital headaches in 92%, visual impairment in 78%, vomiting in 43% and ocular nerves palsies mainly the third nerve palsy in 40% with diplopia and ptosis. Fever, meningeal irritation signs, rhinorrhea and epistaxis were reported in 8%. Predisposing factors were diabetes in 31%, bromocriptine use in 22%, antithrombotic medication in 4.3% and pregnancy in 4.3%. Pituitary imaging showed macroadenomas in all cases. These macroadenomas invade the optical chiasma in 87%, the cavernous sinuses in 48%, the sphenoidal sinus in 39% and have multidirectional extension in 22%. Areas of intratumoral hemorrhage were evident on MRI in 94%. Endocrine evaluation showed at least one hormone deficiency in 92%. Gonadotroph deficiency was present in 78%, corticotroph deficiency in 70% and thyrotropic deficiency in 61%. After the apoplexy episode 40% of GH-secreting adenomas normalized their GH–IGF1 levels and 27% of prolactinomas normalized their prolactin levels. Six patients were treated with high dose glucocorticoids with complete neuro-ophthalmological recovery in 67%.
Conclusion
Pituitary apoplexy is a rare life-threatening clinical syndrome caused by infarction or hemorrhage within a pituitary adenoma, once diagnosed a multidisciplinary team approach is mandatory in order to improve the outcome of this condition.

DOI: 10.1530/endoabs.37.EP1105

EP1106

Relationship between thrombotic markers, insulin resistance and thyroid volume in women with prolactinoma

Ayten Oguz[1], Dilek Tuzun[1], Murat Sahin[1], Elif Inanc[2], Irem Gokalp[2], Didem Atay[2], Hakan Demir[2] & Kamile Gul[1]
[1]Department of Endocrinology and Metabolism, Kahramanmaras Sutcu Imam University, Faculty of Medicine, Kahramanmaras, Turkey; [2]Department of Internal Medicine, Kahramanmaras Sutcu Imam University, Faculty of Medicine, Kahramanmaras, Turkey.

Aim
Hyperinsulinaemia is frequent finding in patients with hyperprolactinemia and has associations with thyroid volume. In this study, we evaluated the association between thrombotic markers, insulin resistance, CIMT, and thyroid volume in female patients with prolactinoma.
Material and methods
38 women with prolactinoma and 24 healthy women were included to the study. We evaluated anthropometric, biochemical, hematologic and hormonal parameters as well as thyroid volume (TV) and CIMT in prolactinoma patients (before treatment) and controls. Insulin resistance was calculated using the HOMA-IR.
Results
Mean age, BMI, TSH, mean platelet volume (MPV) and platelet distribution width (PDW) levels were similar between groups ($P>0.05$). HOMA-IR, platelet counts, prolactin, insülin levels, CIMT and tiroid volume was were significantly higher in prolactinoma group ($P<0.05$). While there was positive correlation between prolactin levels and insulin levels, platelet counts, CIMT and triglyceride levels ($P=0.04$, $r=0.23$; $P=0.01$, $r=0.32$; $P=0.02$, $r=0.28$; $P=0.01$, $r=0.31$, respectively), there was no significant correlation between prolactin levels and TV, MPV, PDW, and HOMA-IR ($P>0.05$). There was statistically significant positive correlation between TV and HOMA-IR, insulin levels, platelet counts and CIMT ($P=0.00$, $r=0.45$; $P=0.00$, $r=0.43$, $P=0.00$, $r=0.35$, respectively).
Conclusion
Hyperprolactinemia has been implicated in the pathogenesis of obesity and glucose intolerance and is reportedly associated with an impaired metabolic profile. Additionally, elevated PRL levels may increase the risk of developing atherothrombotic events via the activation of platelets. Thyroid volume has been found to be associated with age, anthropometry, smoking, iodine status and hyperinsulinaemia. Additonally, growth hormone and growth factors have been shown to affect TV. In our study, we determined relationship between TV and insulin resistance, platelet count, and CIMT in patients with prolactinoma. So we think that, insulin resistance and thrombotic factors may be responsible for change in thyroid volume in patients with prolactinomas.

DOI: 10.1530/endoabs.37.EP1106

EP1107

Gastrointestinal stromal tumour in a patient with multiple endocrine neoplasia type 1

Murat Sahin[1], Ayten Oguz[1], Dilek Tuzun[1], Ilhami Taner Kale[2], Cansu Yilmaz Cabioglu[3], Muharrem Bitiren[4], Safa Ersen Ganidagli[3], Tugba Yilmaz[3] & Kamile Gul[1]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey; [2]Department of General Surgery, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey; [3]Department of Internal Medicine, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey; [4]Department of Pathology, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey.

Introduction
Multiple endocrine neoplasia type-1 (MEN-1) is an autosomal dominant disorder MEN-1 diagnosis is established as the occurrence of two or more MEN-1 associated tumour or one MEN-1 associated tumour in a patient that have 1 MEN-1 family member or positive MEN-1 genetic mutation. MEN-1 associated tumours usually involve the parathyroid glands, anterior pituitary and enteropancreatic cells but many other tumours may be seen. In this report, we presented a gastrointestinal stromal tumour (GIST) in a patient with MEN-1.
Case
A first degree relative of a patient that has MEN-1 was hospitalised to our clinic for screening MEN-1 related tumours. The patient has stomach ache for 6 months and a history of gastric surgery for perforation 9 years ago. In his family history one brother was diagnosed as MEN-1 (parathyroid adenoma, Cushing's disease, gastric neuroendocrine tumour, pancreatic mass and positive MEN gene mutation) and other siblings are under evaluation for MEN-1 associated tumours. In physical examination palpation of abdomen revealed a mass in epigastrium and other findings were normal. Laboratory results were as follow; calcium 10.8 mg/dl (8.4–10.2), phosphor 1.7 mg/dl (2.4–5.4), cortisol 23.88 μg/dl (5–23), prolactine 19.7 ng/ml (3–23), IGF1 152 ng/dl (11–836), TSH 1.57 μIU/ml (0.4–4.2), fT_4 0.91 ng/dl (0.8–2.7), gastrin 57.2 pmol/l (6.2–54.8), insulin 6.92 μIU/ml (6–27) and cortisol after low dose dexamethasone suppression test 1.45 μg/dl. Parathyroid ultrasound showed a hypoechoic solid mass in posterior of the left thyroid lobe, suggestive for parathyroid adenoma. Abdomen CT showed a 112×73 mm solid mass. General surgery performed a biopsy and pathologic examination revealed a GIST.
Conclusion
GISTs are neoplasms arising from connective tissue located in the gastrointestinal wall. GISTs are uncommon neoplasms for MEN-1 syndrome and only a few cases are reported. It is not clear whether GISTs are coincidental or there is a role of MEN-1 gene mutation in these tumours.

DOI: 10.1530/endoabs.37.EP1107

EP1108

The micropenis: about a series of 30 patients

Hakima Abes[1], Nora Soumeya Fedala[1], Ali El Mahdi Haddam[2], Leyla Ahmed Ali[1], Farida Chentli[1] & Djamila Meskine[2]
[1]Bab El Oued Hospital, Algiers, Algeria; [2]Bologhine Hospital, Algiers, Algeria.

Introduction
Micropenis is defined as a stretched penile length of <2.5 S.D., which can be diagnosed from birth to adolescence. It is idiopathic or associated with a chromosomal abnormality, hypogonadism, pituitary abnormality or a complex malformation syndrome. The therapeutic management of this disease should be early to get a favorable response and absence of impact objective. Clarify the clinical and etiological aspects of micropenis of patients followed.
Population, methodology
We made a retrospective study of the cases of patients with micropenis collected in 26 years. A clinical examination and oriented paraclinical exploration has been made.
Results
30 patients were identified (18 children and adolescents between 2–18ans and 12 adultes between 21–44 years). The average age at the consultation is 15 years in children, 30 adults. It is isolated in 50% diagnose at an average age of 13, 5 years in children. In half of the cases, it is associated with other genital abnormalities who did reveal: it in children: cryptorchidism 12 (40%) diagnosed at 5 years (only on at birth) lifts testicles: 2 (6%), hypospadias 1 (3%). The reason for consultation was the signs of hypogonadism in adults in all cases. Aetiological, it is due to a central hypogonadism (40%), GH deficiency (7%) and gonadal dysgenesis (3%). 50% of cases are idiopathic. In half of cases micropenis children (mainly idiopathic and pituitary) responded favourably to androtardyl and GHR in the case of GH deficiency. The younger children (<6 years) responded best.
Discussion and conclusion
The absence of systematic examination of the external genitalia at birth and ignorance of these abnormalities explain the delay in diagnosis and ineffectiveness of treatment. Progress height-weight and hairiness induced by the treatment did not reconsider the treatment against the benefit obtained.

DOI: 10.1530/endoabs.37.EP1108

EP1109

Papillary thyroid carcinoma in a patient with MEN 1 syndrome

Alina Dumitru, Diana Paun, Adina Dragomir, Mihaela Nistor, Georgiana Taujan & Constantin Dumitrache
National Institute of Endocrinology C. I. Parhon, Bucharest, Romania.

Introduction
MEN1 is a rare syndrome characterised by hyperplasia or neoplasm of the parathyroid glands, pituitary, pancreas or duodenum and can associate, less frequently, phaeochromocytoma, thymic or bronchial carcinoids, multiple lipomas, cutaneous angiofibromas and thyroid adenomas.
Case report
A 47-year-old woman with MEN1 presenting parathyroid recurrent adenomas, a pituitary prolactin-growth hormone cosecreting macroadenoma, associated with an incidentall papillary thyroid microcarcinoma. The patient had a primary hyperparathyroidism treated 12 years ago, diagnosed after she was treated for a coraliform lithiasis. 2 years after, a secondary amenorrhea followed, caused by pituitary prolactin secreting macroadenoma, and a dopamine agonist was started. She didn't present for the follow ups for 10 years, when another kidney stone was discovered. Laboratory results show hypercalcaemia and increased PTH, with normal TSH and free thyroxine levels. She had a total thyroidectomy and parathyroidectomy. Besides the two parathyroidian adenomas, the histopathological examination revealed a papillary thyroid microcarcinoma. 1 year after, she was admitted in our service. Having a MEN1 patient, we had to continue the investigation. We found a slightly increased PTH level with normal calcaemia most probably secondary to the vitamin D insufficiency. The pituitary check-up showed a 1.01/1.03 cm adenoma with increased prolactin level and surprisingly increased IGF1 levels. Additionally, the patient had no signs or symptoms suggesting a pancreatic-duodenal involvement (no hypoglycaemia, insulin and gastrin in normal range). The next steps are the genetic analysis for MEN1 gene and the treatment for the pituitary macroadenoma.
Conclusion
This case underline the different phenotypic presentation of MEN1. Our patient had the classical presentation hypercalcaemia but she doesn't associate duodenoenteropancreatic NETs, the second most common endocrine manifestation in MEN1 syndrome. Additionally, the pituitary adenoma cosecrete prolactin and growth hormone. As we found in literature, the papillary thyroid carcinoma is probably incidental.

DOI: 10.1530/endoabs.37.EP1109

EP1110

Breast cancer and gonadal axis in postmenopausal and premenopausal women: impact of obesity

Rym-Ikram Mehaoudi[1], Karima Assas[1], Nawel Lazdam[1], Saida Adane[2] & Yacine Soltani[1]
[1]Faculty Of Biological Sciences, Laboratory of Biology and Physiology of Organisms, Endocrinology Team, USTHB, Algiers, Algeria; [2]Department of Oncology, Central Military Hospital, Ain Naadja, Algiers, Algeria.

Introduction
Breast cancer is one of the diseases causing the most deaths in women worldwide. Obesity, especially in postmenopausal women is a definite risk factor due to hormonal imbalance mainly to the levels of circulating oestrogen. The aim was to record levels for some gonadal axis hormones in breast cancer treated obese women.
Patients and methods
81 women aged between 21 and 80 years 54 are diagnosed with breast cancer (BC) during postmenopausal (PoBC) and premenopausal (PrBC) under different treatments, and 27 pre and postmenopausal women constitute the control groups (PrC and PoC). BMI lipidaemia, inflammatory status established by agglutinated plasma C-reactive protein (CRP) test, plasma LH, FSH, oestradiol, DHEA-S, androstenedione, prolactin, and testosterone were estimated by RIA.
Results
Obesity is predominant in PoBC group with 50 vs 35% in PrBC. while overweigh-obese women group represents 72% of PrBC and 83% PoBC groups respectively. Obesity in PoBC patients was mainly associated to dyslipidaemia, including significant increase in plasma total cholesterol, LDL-c, TG and HDL-c decrease. FSH increase in PrBC (126.3%; $P=0.01$) and decrease in PoBC (3.8%) was concomitant to DHEA-S fall in PrBC (42.8%; $P=0.037$) and increase in PoBC (51.3%; $P=0.031$) vs control groups. Whereas LH and estradiol increased concomitantly in PrBC (14.9 and 13.8%), but decreased (40.5 and 3.8%) in PoBC, testosterone was significantly reduced in regrouped PrBC and PoBC patients (24.2%; $P=0.04$). while androstenedione and prolactin fall of 17.5 and 11.9% respectively in regrouped PrBC and POBC patients.
Discussion conclusion
Obesity is confirmed as breast cancer risk factor in postmenopausal women. The sensitivity to hormone therapy appear to be more efficient in PoBC women with BMI$\leq$30 compared to PrBC patients, and reveal their efficiency to decrease plasma oestradiol, leading to activate positive feedback mechanism on LH and FSH secretion.
Disclosure
This work was supported by financial help from Algerian National Research Program (PNR).

DOI: 10.1530/endoabs.37.EP1110

EP1111

Neuroendocrine tumours observed in endocrinology

Mounia Safer[1], Nora Soumeya Fedala[1], Ali El Mahdi Haddam[2], Leyla Ahmed Ali[1], Farida Chentli[1] & Djamila Meskine[2]
[1]Bab El Oued Hospital, Algiers, Algeria; [2]Bologhine Hospital, Algiers, Algeria.

Introduction
Neuroendocrine tumours or TNE form from cells of the endocrine and neurological system at any point in the body and are characterised by their ability to secrete hormones and express protein markers. They are often benign, but some are malignant and can easily metastasise.
Objective
To describe the clinical, paraclinical and scalable of TNE endocrinology observed outside medullary carcinoma and phaeochromocytoma.
Population, methodology
Retrospective study of cases of patients with NETs collected in 26 years. All patients have benefited from a clinical, hormonal balance, specific morphological investigation and postoperative follow-up.
Results
16 cases were observed. They represented by endocrine pancreatic tumours ($n=10$, 62.25%) and carcinoids ($n=6$; 37.5%). The mean age at diagnosis was 43 ± 15 years (7–78 years) and sex ratio 1H/2F. 66.6% of pancreatic secreting tumours and revealed by an endocrine syndrome (60% insulinoma, 6.6% secrete TCT) and 33.3% non-secreting tumours discovered during abdominal pain. Average tumour size was 24 ± 0.4 mm (1 ± 0.4 cm: insulinoma and 7 ± 1 cm other PET). 46% are malignant (size$>$ 2 cm; 13% insulinoma; 33% others), 26% are metastatic, and 50% are well differentiated. The carcinoid are located at

rectum (*n*:2),intestinal (*n*:1), thymus (*n*: 1) and lung (*n*:6). They are malignant, well differentiated with slow evolution. All patients were successfully operated completed by a antisécrétoirs treatment or chemotherapy (10%). No recurrence or deaths were observed.

Discussion and conclusion

NET are rare in endocrinology. They dominate the gastrointestinal system. They are often secreting and malignant tumours with slow-growing and generally good prognosis. Their medical management requires a multidisciplinary team and a long term follow up.

DOI: 10.1530/endoabs.37.EP1111

EP1112

Vitamin D and breast cancer

Ifigenia Kostoglou-Athanassiou[1], Eustathia Papageorgiou[2], Athanasios Armakolas[2] & Michael Koutsilieris[2]
[1]Department of Endocrinology, Red Cross Hospital, Athens, Greece; [2]Department of Experimental Physiology, Medical School, University of Athens, Athens, Greece.

Introduction

The anticancer action of vitamin D is currently considered one of its main properties. The main actions of vitamin D are related to the regulation of calcium levels and the normal function of the musculoskeletal system. However, its anticancer action is currently in the focus of research interests.

Aim

The aim was to study the effect of vitamin D on MCF-7 human breast cancer cells *in vitro*.

Methods

The effect of 1,25 $(OH)_2D_3$ (Sigma-Aldrich) at an initial concentration of 200 nM on MCF-7 human breast cancer cells was studied *in vitro*. MCF-7 human breast cancer cells were incubated for 48 h at a temperature of 37 °C with progressively decreasing concentrations of $1,25(OH)_2D_3$. MCF-7 cells were also incubated with progressively decreasing concentrations of $1,25(OH)_2D_3$ (the initial concentration of $1,25(OH)_2D_3$ being 200 nM) in the presence of the antimitotic agent docetaxel 50 nM.

Results

A mild inhibition of the proliferation of human breast cancer cells MCF-7 was observed after 48 h incubation with $1,25(OH)_2D_3$. After simultaneous incubation with $1,25(OH)_2D_3$ and docetaxel intense inhibition of the proliferation of MCF-7 breast cancer cells was observed.

Conclusions

In conclusion, a mild inhibitory effect of $1,25(OH)_2D_3$ on the proliferation of MCF-7 human breast cancer cells was observed, while the antimitotic agent docetaxel had intense inhibitory effect on their proliferation. These findings are in agreement with the expression of VDR (Alimirah *et al.*, Mol Cell Biochem, 2010), the vitamin D receptor, in breast cancer cells.

DOI: 10.1530/endoabs.37.EP1112

EP1113

The effect of melatonin on MCF-7 breast cancer cells in vitro

Ifigenia Kostoglou-Athanassiou[1], Eustathia Papageorgiou[2], Athanasios Armakolas[2] & Michael Koutsilieris[2]
[1]Department of Endocrinology, Red Cross Hospital, Athens, Greece; [2]Department of Experimental Physiology, Medical School, University of Athens, Athens, Greece.

Introduction

It has been reported that blind women with disturbed melatonin secretion have a lower incidence of breast cancer. A higher incidence of breast cancer has been reported in women in shift work, in which lower nocturnal melatonin secretion is observed. The anticancer action of melatonin is currently the focus of research interest.

Aim

The aim was to study the effect of melatonin on MCF-7 breast cancer cells *in vitro*.

Methods

The effect of melatonin (Sigma-Aldrich) at an initial concentration of 1nM on MCF-7 human breast cancer cells was studied *in vitro*. MCF-7 human breast cancer cells were incubated for 48 h at a temperature of 37 °C with progressively decreasing melatonin concentrations. MCF-7 cells were also incubated for 48 h with progressively decreasing melatonin concentrations in the presence of the antimitotic agent docetaxel 50 nM.

Results

The proliferation of MCF-7 human breast cancer cells was significantly inhibited by melatonin. The antimitotic agent docetaxel significantly inhibited the proliferation of MCF-7 cells. The simultaneous incubation of MCF-7 cells with melatonin and docetaxel had a synergistic inhibitory effect on their proliferation.

Conclusions

In conclusion, it appears that melatonin exerts an inhibitory effect on the proliferation of breast cancer cells *in vitro*. These findings should be confirmed in other cell lines and are in agreement with findings of other researchers having shown the presence of the melatonin receptor MT1[1] on the cell surface of breast cancer cells.

Reference

1. Jablonska K, Pula B, Zemla A, Owczarek T, Wojnar A, Rys J, Ambicka A, Podhorska-Okolow M, Ugorski M, Dziegiel P. Expression of melatonin receptor MT1 in cells of human invasive ductal breast carcinoma. *J Pineal Res* 2013; **54**:334–45.

DOI: 10.1530/endoabs.37.EP1113

EP1114

The effect of melatonin on pC3 prostate cancer cells *in vitro*

Ifigenia Kostoglou-Athanassiou[1], Eustathia Papageorgiou[2], Athanasios Armakolas[2] & Michael Koutsilieris[2]
[1]Department of Endocrinology, Red Cross Hospital, Athens, Greece; [2]Department of Experimental Physiology, Medical School, University of Athens, Athens, Greece.

Introduction

Melatonin is an indole being produced by the pineal gland and secreted mainly during the night. Melatonin is involved in the regulation of biological rhythms. The hormone possesses antioxidant action and is thought to be involved in the protection of the organism from the development of malignant tumors. Melatonin has been found to have anticancer action *in vitro* as is has been observed to inhibit the proliferation of cancer cells *in vitro*.

Aim

The aim was to study the effect of melatonin on PC3 prostate cancer cells *in vitro*.

Methods

The effect of melatonin (Sigma–Aldrich) at an initial concentration of 1nM on PC3 prostate cancer cells *in vitro* was studied. PC3 cells were incubated *in vitro* for 48 h at a temperature of 37 °C with progressively decreasing melatonin concentrations. PC3 cells were also incubated for 48 h with progressively decreasing melatonin concentrations in the presence of the antimitotic agent docetaxel 50 nM.

Results

The proliferation of PC3 prostate cancer cells was significantly inhibited by melatonin. In the simultaneous presence of melatonin and docetaxel the inhibitory effect on the proliferation of PC3 cells was very significant.

Conclusions

In conclusion, it appears that melatonin has an inhibitory effect on the proliferation of prostate cancer cells *in vitro*. These findings need to be confirmed in various other cancer cell lines and are in agreement with other research findings having shown the anticancer effect of melatonin. It appears that the modern way of life which disturbs the biological rhythms controlled by the cycle of light and inadvertently exposes the human organism to light during the night may contribute to carcinogenesis.

DOI: 10.1530/endoabs.37.EP1114

EP1115

Multifocal insulinomas (insulinomatosis) in GLP-1-receptor PET/CT

Stefan Jenni[1], Kwadwo Antwi[2], Melponemi Fani[2], Damian Wild[2], Tobias Heye[3], Beat Gloor[4], Aurel Perren[5] & Emanuel Christ[1]
[1]Departement of Endocrinology, Diabetes and Clinical Nutrition, Inselspital, University Hospital, University of Bern, Bern, Switzerland; [2]Division of Nuclear Medicine, University of Basel Hospital, Basel, Switzerland; [3]Clinic of Radiology and Nuclear Medicine, University of Basel Hospital, Basel, Switzerland; [4]Division of Visceral Surgery, University Hospital of Bern, Inselspital, Bern, Switzerland; [5]Institute of Pathology, University of Bern, Bern, Switzerland.

Introduction
Apart from occurring sporadically, insulinoma within the framework of multiple endocrine neoplasia 1 (MEN-1) is well known. The rare presence of multifocal insulinomas has recently been assigned a separate entity (insulinomatosis). The difficulty of localising insulinomas may be improved by GLP1-receptor imaging. Case report A 48-year-old woman had been treated for suspected epileptic seizures for 2 years (lamotrigine). During another such episode low blood glucose (BG) was detected. During fasting she was unaware of hypoglycaemia (BG 2.3 mmol/l), endogenous hyperinsulinism was established. With a history of treated prolactinoma (operation, quinagolid) – and slightly elevated calcium levels MEN-1 was considered. ^{68}Ga-DOTA-Exendin-4 PET/CT and MRI revealed a major lesion located directly left to the pancreatic head (8×13 mm) and smaller lesions in the tail (max. 5 mm). After pretreatment with diazoxid/prednisolone surgery was proposed. Intraoperatively, granular pancreatic tissue was palpated mainly located in the left side up to the head of the pancreas – matching with the increased uptake in GLP-1R imaging. As intraoperative ultrasound did not confirm a focal lesion, left-sided pancreatectomy was performed. Histologically the major lesion proved to be insulin-positive, however 37 more small adenoma, mainly with insulin staining were detected establishing the diagnosis of insulinomatosis. The postoperative course was complicated by a peripancreatic abscess and recurrence of asymptomatic mildly low BG levels. Genetic testing (MEN-1) is pending.
Conclusions
i) GLP-R imaging is useful in benign insulinomas and might be useful in the context of MEN-1 in order to separate insulin secreting neuroendocrine tumours (NET) from other secreting and non-secreting NETs, ii) GLP-1R imaging showed positive lesions in the case of insulinomatosis. However, most of the lesions were too small to be detected by ^{68}Ga-DOTA-Exendin-4 PET/CT. iii) Clinical and biochemical work-up of this patient suggests that insulinomatosis occurred in the context of MEN-1 that – if confirmed – would be a new association.

DOI: 10.1530/endoabs.37.EP1115

EP1116

Expression analysis of potentially MEN1-targeting microRNAs in sporadic and MEN-1 syndrome associated parathyroid adenomas and hyperplasias

Vince Kornél Grolmusz[1,2], Katalin Borka[3], Katalin Balogh[1], Anna Szentpéteri[1], Csaba Dékány[3], András Kiss[3], Zsuzsanna Valkusz[4], Miklós Tóth[1], Anikó Somogyi[1], János Horányi[5], Károly Rácz[1,6] & Attila Patócs[2,6]
[1]2nd Department of Medicine, Semmelweis University, Budapest, Hungary; [2]'Lendület' Hereditary Endocrine Tumours Research Group, Hungarian Academy of Sciences – Semmelweis University, Budapest, Hungary; [3]2nd Department of Pathology, Semmelweis University, Budapest, Hungary; [4]1st Department of Medicine, University of Szeged, Szeged, Hungary; [5]1st Department of Surgery, Semmelweis University, Budapest, Hungary; [6]Molecular Medicine Research Group, Hungarian Academy of Sciences – Semmelweis University, Budapest, Hungary.

Background and aim
Primary hyperparathyroidism (PHPT) is a frequent endocrinopathy among postmenopausal women, leading to hypercalcaemia, osteoporosis and nephrolithiasis. PHPT may represent the first manifestation of certain familial syndromes. Among these, multiple endocrine neoplasia syndrome type 1 (MEN-1) caused by germline mutation of *MEN1*, the gene encoding menin, is the most frequent. Additionally, somatic mutations of *MEN1* and microRNAs silencing *MEN1* have also been proposed to be involved in sporadic parathyroid tumourigenesis. Our aim was to determine if there is a difference in expression of potentially *MEN1*-targeting microRNAs between MEN-1 syndrome associated and sporadic PHPT tissues.
Materials and methods
In silico analysis was performed to detect microRNAs potentially targeting *MEN1*. Immunohistochemical analysis of menin and Ki67 was performed in 16 MEN-1 associated and 41 sporadic PHPT tissues. RNA was isolated from formalin-fixed, paraffin-embedded PHPT tissues and microRNA expression analysis of six chosen microRNAs was performed using predesigned TaqMan probes for quantitative PCR. *MEN1* status was determined by Sanger sequencing. Statistical analysis was performed using IBM SPSS Statistics Software.
Results
All MEN-1 associated as well as 12 (29.3%) sporadic PHPT tissues lacked nuclear menin expression on immunohistochemical analysis. MicroRNA analysis revealed that hsa-miR-24 and hsa-miR-28 levels were elevated in sporadic PHPT tissues compared to those measured in MEN-1 associated tissues ($P=0.011$ and $P=0.019$, respectively).
Conclusions
Elevated levels of microRNAs potentially targeting *MEN1* detected in sporadic PHPT tissues might contribute to the silencing of menin during sporadic parathyroid tumourigenesis.
Acknowledgement
The authors acknowledge the financial support from Hungarian Scientific Research Fund (OTKA, PD100648 (AP)) and Technology Innovation Fund, National Developmental Agency (KTIA-AIK-2012-12-1-0010).
Disclosure
The authors acknowledge the financial support from Hungarian Scientific Research Fund (OTKA, PD100648 (AP)) and Technology Innovation Fund, National Developmental Agency (KTIA-AIK-2012-12-1-0010).

DOI: 10.1530/endoabs.37.EP1116

EP1117

Vitamin D and prostate cancer

Ifigenia Kostoglou-Athanassiou[1], Eustathia Papageorgiou[2], Athanasios Armakolas[2], Vlasia Aroni[2] & Michael Koutsilieris[2]
[1]Department of Endocrinology, Red Cross Hospital, Athens, Greece; [2]Department of Experimental Physiology, Medical School, University of Athens, Athens, Greece.

Introduction
Vitamin D is a hormone related to calcium homeostasis and normal function of the musculoskeletal system. Recently, the extraskeletal actions of vitamin D are the focus of scientific interest. The hormone is thought to possess anticancer properties, these properties being especially related to cancer of the prostate.
Aim
The aim was to study the effect of vitamin D on PC3 prostate cancer cells *in vitro*.
Methods
The effect of $1,25(OH)_2D_3$, $25(OH)D_3$, $1\alpha(OH)D_3$ and paricalcitol at initial concentrations of 200, 40, 20 and 20 nM, respectively, on PC3 prostate cancer cells was studied *in vitro*. PC3 cells were incubated for 48 h at 37 °C with progressively decreasing concentrations of $1,25(OH)_2D_3$, $25(OH)D_3$, $1\alpha(OH)D_3$ and paricalcitol. Experiments were also performed with $1,25(OH)_2D_3$ at concentrations of 500 nM and 1 μM. PC3 cells were also incubated with progressively decreasing concentrations of $1,25(OH)_2D_3$, the initial concentration being 200 nM, in the presence of the antimitotic agent docetaxel 50 nM.
Results
The proliferation of PC3 prostate cancer cells was not affected by $25(OH)D_3$, $1\alpha(OH)D_3$ and paricalcitol. High concentrations of $1,25(OH)_2D_3$ mildly inhibited PC3 proliferation whereas lower concentrations had no effect. The proliferation of PC3 cells was inhibited in the presence of both $1,25(OH)_2D_3$ and docetaxel.
Conclusions
In conclusion, $25(OH)D_3$ and analogues of vitamin D had no effect on the proliferation of PC3 prostate cancer cells. However, relatively high concentrations of the active hormone $1,25(OH)_2D_3$ was shown to inhibit PC3 cells proliferation. It appears, that vitamin D may possess anticancer properties especially related to prostate cancer.

DOI: 10.1530/endoabs.37.EP1117

EP1118

Oestrogen- and progesterone-receptors may play a role in the pathogenesis of gastroenteropancreatic neuroendocrine tumours

Nadine Zimmermann[1], Georg Brabant[2], Nehara Begum[3] & Christoph Thorns[1]
[1]Institut für Pathologie, Universität zu Lübeck, Lübeck, Germany; [2]Medizinische Klinik 1, Universität zu Lübeck, Lübeck, Germany; [3]Klinik für Chirurgie, Universität zu Lübeck, Lübeck, Germany.

A positive expression of oestrogen-receptors has recently been demonstrated in pancreatic neuroendocrine tumours as well as in non-neoplastic islet-cells. This prompted us to systematically analyse the expression of both oestrogen and progesterone receptors in a series of GEP neuroendocrine tumours. We analysed

oestrogen- and progesterone-receptor in 69 foregut GEP, 25 midgut GEP and seven hindgut GEP. Namely, the foregut GEP included 53 pancreatic NET. All tumour samples were evaluated by to pathologist and a consensus immunoreactivity score according to Remmele (0–12) was assigned. An immunoreactivity score ≥ 2 was regarded as positive. According to the definition above 17% of the samples were oestrogen-receptor and 46% were progesterone-receptor positive. When we compared pancreatic NET to all other GEP-NET as well as to foregut, midgut and hindgut NET, the expression of oestrogen-receptor did not differ significantly between the groups. However, expression of the progesterone-receptor was more frequently expressed in pancreatic NET than in the other GE-NET (81% vs 8%, $P<0.0001$). This difference remained statistically significant, when pancreatic NET were compared to foregut NET (81% vs 13%, $P<0{,}0001$), to non-pancreatic midgut NET (81% vs 8%, $P<0{,}0001$) and to hindgut NET (81% vs 14%, $P=0{,}0039$). To evaluate the potential role of oestrogen/progesterone receptors in metastasis we evaluated biospies of 83 metastases from 45 cases. Oestrogen-receptor expression was rare (IRS ≥ 2 in three nodal metastases of pNET and four nodal metastases of non-pNET). In contrast, progesterone-receptor expression was found in only one nodal metastases of non-pancreatic origin, but 15 metastases of pNET stained positive for the progesterone receptor. In summary, our data indicate a potential role of progesterone-receptor expression in the metastatic process and its determination may help to identify the primary in cases of NET-metastasis of unknown primary.

Disclosure
The study was supported by an unrestricted educational grant from IPSEN Pharma GmbH (Ettlingen), Germany.

DOI: 10.1530/endoabs.37.EP1118

EP1119

Audit of patients with multiple endocrine neoplasia type 1 (MEN1): screening of pancreatic neuroendocrine tumours (pNETs), parathyroid tumours and pituitary adenomas

Ma Pyeh Kyithar[1], Lisa Cullen[2], Chun Lee[2], Niall Swan[2], Justin Geoghegan[2], Stephen Skehan[2], Rachel Crowley[1,2], Donal O'Shea[1,2] & Dermot O'Toole[2]
[1]Endocrinology Department, St Vincent's University Hospital, Dublin, Ireland; [2]Neuroendocrine Tumour Service, St. Vincent's University Hospital, Dublin, Ireland.

Introduction
Patients with MEN1 have increased morbidity and mortality compared to those patients with sporadic NETs. No genotype-phenotype correlation is described and age-related clinical penetrance surpasses 50 and 90% by 20 and 40 years, respectively. The aim of the audit was to compare the screening programme for MEN1 patients with MEN1 clinical guidelines.
Methods
Case notes of MEN1 patients attending a tertiary NET-multidisciplinary team (MDT) in Ireland were reviewed. All patients attending the NET-MDT have gastrointestinal hormone, parathyroid, pituitary profiles, endoscopic and imaging studies according to guidelines (NIH 2012, Brandi *et al*. 2001; 86: 5658–71).
Results
Of 13 patients with MEN1 (11 kindreds), 85% ($n=11$) had confirmed *MEN1* mutations and two had clinical or familial MEN1. 69% were referred to NET-MDT for screening due to known *MEN1* mutations, 15% for family screening, 8% for management of pNETs and 8% for screening due to primary hyperparathyroidism and acromegaly. Prior to NET-MDT assessment, 46% did not have endoscopic/radiology studies to screen for pNETs and none of the patients had CT/MRI thorax to screen for thymic/bronchial NETs. Mean age referred to NET-MDT was 41.5 ± 12.2 years. Mean age at endoscopic/radiological screening for NETs (prior to/at NET-MDT) was 37.1 ± 14.3 years. Mean age at diagnosis of NETs was 34.9 ± 14.3 years. On screening of 13 patients at NET-MDT, the following new diagnoses were made: eight pNETs, seven duodenal/gastric NETs, two primary hyperparathyroidism, three pituitary adenomas and four adrenal adenomas. Family screening has been performed in 8/11 families: a further seven family members were identified with *MEN1* mutations and will attend NET-MDT for screening. Genetic screening of other families is proceeding.
Conclusion
Endoscopic/radiological screening of NETs occurred at later age than recommended by current guidelines. Surveillance methods were also largely at variance with guidelines. Referral to a dedicated MDT has identified a significant number of previously unrecognised neuroendocrine pathologies.

DOI: 10.1530/endoabs.37.EP1119

EP1120

The prevalence of benign and malignant neoplasms in the patients with acromegaly

Adam Stangierski, Kosma Wolinski, Edyta Gurgul & Marek Ruchala
Department of Endocrinology, Metabolism and Internal Medicine, Poznan University of Medical Sciences, Poznan, Poland.

Introduction
Acromegaly is a relatively rare endocrine condition caused by GH oversecretion by pituitary adenoma. Its most frequent complications include cardiovascular and respiratory system diseases with high tendency of neoplastic transformation and increased risk of benign and malignant tumors. The aim of this retrospective study was to assess the prevalence of benign and malignant neoplasms in patients with acromegaly.
Materials and methods
We have searched the medical documentation of patients treated in our medical center from the years 2004–2013. The prevalence of benign and malignant neoplasms was analysed basing on the latest available records of particular patients.
Results
We have identified 180 patients with acromegaly (108 women, 72 men). The mean age at the time of last available assessment was 52.5 years (S.D. 12.2, median – 54.0). The most common neoplastic comorbidity was observed in the thyroid -140 patients (77.8%) – 110 patients with multinodular goiter (MNG) (61.1%) or resection of MNG in the past medical history. Adrenal adenomas were diagnosed in nine subjects (5%), prostate hyperplasia in six (8.3% of males), and polyps of the colon in 1.7% of all individuals. Among malignancies, the most common were thyroid cancer ($n-11$, 6.1%), breast cancer ($n=5$, 4.6% of women with acromegaly) and colonic cancer ($n=4$, 2.2%).
Conclusions
Patients with acromegaly present increased risk of neoplastic transformation, especially in the thyroid, adrenals, gastrointestinal tract and prostate. Among malignancies, thyroid, breast and colonic cancer were the most frequent. According to our results, active screening for potential malignancies should be an important part in the management of acromegaly.

DOI: 10.1530/endoabs.37.EP1120

EP1121

Identification of human SST2 somatostatin receptor domains involved in receptor internalization and signaling in pancreatic neuroendocrine tumors

Valeria Cambiaghi[1], Eleonora Vitali[1], Giovanna Mantovani[2], Anna Spada[2], Erika Peverelli[2] & Andrea Lania[1,3]
[1]Laboratory of Cellular and Molecular Endocrinology, IRCCS Clinical and Research Institute Humanitas, Rozzano, Italy; [2]Endocrine Unit, Department of Clinical Sciences and Community Health, Fondazione IRCCS Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; [3]BIOMETRA Department, University of Milan, Neurosurgery Department, IRCCS Humanitas Clinical Institute, Rozzano, Italy.

Somatostatin exerts its inhibitory effects on hormone secretion and cell proliferation via five receptors subtypes (SST1-SST5). After agonist binding, receptor residues mainly located in the carboxyl terminal (CT) and in the third intracellular loop (IC3) are phosphorylated and β-arrestins are recruited to drive SSTRs internalization.
Aim of the study is to characterize the intracellular mechanisms responsible for SST2 internalization and identify the molecular determinants mediating its intracellular signaling in pancreatic neuroendocrine QGP1 cell line. To this purpose we created SST2 receptor mutants, the first lacking 20 aminoacids in CT portion (del349), the second a IC3 mutant with a point mutation (Ser-245-Ala) in a phosphorylation site. We evaluated SST2 mutants ability to associate with β-arrestins and to internalize after SST2 selective somatostatin analog stimulation (BIM23120). In cells transfected with the SST2 IC3 mutant, no differences in β-arrestins recruitment and receptor internalization were observed after SST2 activation in comparison with cells bearing wild type SST2. Conversely, the truncated SST2 failed to recruit β-arrestins and to internalize after BIM23120 incubation. Then, we analyzed the effect of BIM23120 on cell proliferation, cyclin D1 expression and ERK1/2 phosphorylation in the presence of either IC3 mutant and truncated SST2. As expected, BIM23120 induced a reduction in cell proliferation ($-30\pm7\%$, $P<0.01$ vs untreated) and in CD1 expression ($-23\pm8\%$, $P<0.001$ vs untreated) in SST2 wild type QGP1 transfected cells, this effect being completely lost in the presence of both SST2 mutants. To further

analyze the antiproliferative actions of SST2, we analyzed the effects of SST2 activation on ERK1/2 phosphorylation and we found the both SST2 mutants fail to affect ERK1/2 phosphorylation status after BIM23120 incubation. Taken together these data suggest that: i) CT region is crucial for β-arrestins/SST2 interaction and SST2 internalization; ii) antiproliferative intracellular signaling mediated by SST2 require the integrity of both CT and IC3 domains.

Disclosure
This work was supported by an AIRC (Associazione Italiana Ricerca Cancro - Milan) grant KFR062-2 to A.G.L.

DOI: 10.1530/endoabs.37.EP1121

EP1122

The evaluation of the effectiveness and safety of transarterial embolisation of to the liver metastasised neuroendocrine tumours

Sophie van Dijk, Margot Tesselaar, Wieke Verbeek, Marc Meier & Warner Prevoo
The Netherlands Cancer Institute, Amsterdam, The Netherlands.

Abstract
Transarterial embolisation (TAE) is an effective treatment for liver metastases from neuroendocrine tumour (NET). It reduces arterial blood flow to the tumour resulting in ischemia and necrosis. In this single centre retrospective study the effectiveness and safety of TAE was evaluated.
Patients and methods
30 patients with histological confirmed gastro-entero-pancreatic NET with liver metastases were investigated. Tumour response, decline in symptomatic carcinoid syndrome, the overall survival and adverse events were evaluated in the whole population.
Results
Among 30 patients (15 male) 47 TAE procedures were performed. The median age was 61.5 years. The primary NET site is ileum in 16 patients (53.3%), colon in 6 patients (20%), pancreas in one patient (3.3%), lung in one patient and unknown in six patients. 18 patients (60%) received surgery for their primary NET prior to TAE. 22 patients (73.3%) were also diagnosed with extrahepatic metastases. The number of patients with a decrease in liver tumour on CT were significantly higher when liver involvement before TAE was $<50\%$. 29 patients (96.7%) received octreotide treatment prior to TAE. The median time from diagnosis to first TAE was 36.5 months. There was a significant decrease in chromogranin A both 1 and 3 months after TAE ($P=0.001$ and $P=0.017$, resp.). 80.9% of the cases had a decrease of neuroendocrine liver metastases after TAE. 26 patients had carcinoid syndrome of which 88% had a decrease in clinical symptoms at 1 month follow up. This was 69.6% at 3 months follow up. Liver functions assessed 1 and 3 months after TAE were compared to baseline values. Bilirubin shows a significant decrease at 1 month. Alkaline phosphatase is significantly higher after both 1 and 3 months. γGT is significantly higher at 1 month. ASAT, ALAT and LDH show no significant differences. Two patients had major TAE related complications. No TAE related death occurred. The overall survival at 1 year follow up is 86.7%, which is not statistically different compared to the overall survival of the group of patients who had a second or third TAE.
Conclusion
Transarterial embolisation is a relative safe treatment for to the liver metastasized NET which can be done multiple times within one patient. It reduces carcinoid syndrome and shows a significant reduction in tumour marker. Radiological decrease rate is significantly higher with patients who have less tumours in the liver.

DOI: 10.1530/endoabs.37.EP1122

EP1123

Evaluation of routine basal serum calcitonin measurement for an early diagnosis of medullary thyroid carcinoma

Entela Puca[1], Kadir Burak Koza[1], Emiljana Huti[1], Sonila Bitri[1], Albana Daka[1], Edmond Puca[2] & Agron Ylli[2]
[1]American Hospital 2, Tirana, Albania; [2]UHC Mother Teresa, Tirana, Albania.

Background
Medullary thyroid carcinoma (MTC) is characterised by a high concentration of serum calcitonin. Routine measurement of serum calcitonin concentration has been advocated for detection of MTC among patients with nodular thyroid diseases. The aims of our study were to identify medullary thyroid cancer (MTC) in its earliest stages by screening patients with basal calcitonin measurements and to determine whether basal serum calcitonin measurements should be a part of our routine evaluation of a nodular goitre.
Subject and methods
We performed routine measurement of basal serum calcitonin levels from 151 patients (male 30 and female 121 with nodular goitre. The average age was 47 years old (range 19–76).
Results
Patients with FNAC or ultrasound suspicious of any kind of thyroid carcinoma and patients with elevated basa calcitonin level underwent surgery. Three patients (1.9%) had elevated basal serum calcitonin levels ranging between 129 and 7493 pg/ml. FNAC was suggestive of MTC in two from three patient with elevated calcitonin. MTC was confirmed in all patients, with elevated calcitonin. Differentiated thyroid carcinoma, mostly papillary, was confirmed at histology in 40 subjects. The prevalence of MTC, diagnosed by serum CT measurement among 136 patients with nodular thyroid disease was high: 1.9% of all thyroid nodules and 7% of all thyroid carcinomas. Serum CT measurement was superior to FNAC in suggesting the diagnosis of MTC.
In conclusion, calcitonin measurement is an effective method for the diagnosis of MTC. It is superior to FNAB for diagnosis of MTC. High basal serum calcitonin levels increase the chance of curative therapy by diagnosing it in the early stages.

DOI: 10.1530/endoabs.37.EP1123

EP1124

Evaluation of metabolic syndrome in patients with primary hyperparathyroidism

Mustafa Caliskan[1], Muyesser Sayki Arslan[1], Esra Tutal[1], Selvihan Beysel[1], Melia Karakose[1], Mahmut Apaydin[1], Ozgur Ozcelik[1], Muhammed Kizilgul[1], Nujen Colak Bozkurt[1], Erman Cakal[1], Mustafa Ozbek[1] & Tuncay Delibasi[1,2]
[1]Department of Endocrinology and Metabolism, Diskapi Teaching and Research Hospital, Ankara, Turkey; [2]Hacettepe University, School of Medicine (Kastamonu), Ankara, Turkey.

Aims
Primary hyperparathyroidism (PH) has been reported to be associated with increased insulin resistance, hypertension, dyslipidemia and cardiovascular inflammatory markers. The aims of this study were to evaluate the rate of metabolic syndrome (MS) and effect of parathormone, calcium and phosphorus levels to MS components in PH subjects.
Methods
One hundred and fifty one subjects, 23 men and 128 women, aged 53 ± 11.2 years with newly diagnosed PH were recruited from our outpatient clinic. All subjects underwent measurements of height, weight, waist and hip. Metabolic variables were obtained after an overnight fasting. MS was diagnosed using the Adult Treatment Panel III criteria (ATP III).
Results
The rate of the MS (76/151, 50.3%) was higher to that reported in the general Turkish population (36.6%). 15.2% ($n=23$) of patients had diabetes mellitus and 72.8% ($n=110$) of patients had hypertension. Serum levels of glucose and

Table 1 Demographic parameters in studied group.

Age	53 ± 11.2
Sex (M/F)	23 M/128 F
Glucose (mg/dl)	95.2 ± 17.1
Triglyceride (mg/dl)	152.1 ± 73
Calcium (mg/dl)	11.9 ± 0.67
Phosphorus (mg/dl)	2.6 ± 0.47
Parathormone (mg/dl)	253.6 ± 256.9
Metabolic syndrome (%)	50.3
Diabetes mellitus (%)	15.2
Hypertension (%)	72.8
Obesity (%)	52.3
Overweight (%)	35.7

triglyceride were 95.2±17.1 and 152.1±73 mg/dl, respectively. The rate of obesity, overweight was 52.3 and 35.7% respectively. There were no significant differences between the levels of calcium, phosphorus and parathormone levels (11.16±0.8 vs 11.01±0.6 mg/dl, 2.59±0.45 vs 2.63±0.48 mg/dl, 259.6±238 vs 247.5±276 mg/dl respectively) according to MS presence (Table 1).

Conclusion

Based on the results of this study, the rate of the MS in PH was found to be higher than that reported in the general Turkish population. Metabolic control must be considered in the clinical management of patients diagnosed PH.

DOI: 10.1530/endoabs.37.EP1124

EP1125

Mitotane directly interacts with lipid membranes and alters membrane structure and dynamics

Peter Müller[1], Stephan Theisgen[2], Andreas Schirbel[3], Silviu Sbiera[3], Ivan Haralampiev[1], Martin Fassnacht[3,4], Daniel Huster[2] & Matthias Kroiss[3,4]

[1]Humboldt University, Berlin, Germany; [2]Institute of Medical Physics and Biophysics, Leipzig, Germany; [3]University Hospital Würzburg, Würzburg, Germany; [4]Comprehensive Cancer Center Mainfranken, Würzburg, Germany.

Context

Mitotane (1,1-dichloro-2-[o-chlorophenyl]-2-[p-chlorophenyl]ethane) is the only drug approved for treatment of adrenocortical carcinoma (ACC). Mitotane counteracts both tumor growth and tumoural steroid hormone production but treatment is severely hampered by unfavorable pharmacokinetics and serious side effects. Mitotane is a lipophilic compound and treatment emergent alterations of lipid metabolism are frequently observed. This raises the question whether mitotane directly interacts with lipids.

Objective

To investigate the impact of mitotane on lipid membranes using biophysical techniques.

Methods

We used nuclear magnetic resonance (NMR), electron spin resonance (ESR) and fluorescence spectroscopy as well as fluorescence microscopy to determine whether mitotane interacts with lipid membranes. We aimed at determining the impact of mitotane on membrane structure and dynamics by assessing its influence on membrane integrity and on the formation of lateral membrane domains in lipid vesicles (large unilamellar vesicles, giant unilamellar vesicles).

Results

We demonstrate that mitotane intercalates into lipid membranes. This binding influences the mobility of spin-labeled lipids within membranes and disturbs membrane integrity in a dose-dependent manner. The presence of cholesterol in the membrane appears to modulate these effects.

Conclusion

Mitotane directly binds to and interacts with lipid membranes thereby altering membrane structure and dynamics. This interaction may contribute to the biological effects of mitotane impacting both on efficacy and adverse effects.

Disclosure

This work was supported by the Deutsche Forschungsgemeinschaft (grant FA 466/4-1 to M.F. and KR 4371/1-1 to M.K.) and a fellowship of the Comprehensive Cancer Center Mainfranken to M.K.

DOI: 10.1530/endoabs.37.EP1125

EP1126

Oestrogen metabolism by steroid sulphatase and 17β-hydroxysteroid dehydrogenases promotes colorectal cancer proliferation via the G-protein coupled oestrogen receptor

Lorna Gilligan, Habibur Rahman, Anne-Marie Hewitt, Angela Taylor, Dion Morton & Paul Foster

University of Birmingham, Birmingham, West Midlands, UK.

Colorectal cancer (CRC) is the third most common cancer worldwide with incidence expected to rise. Although not traditionally viewed as a hormonal cancer, evidence suggests peripheral synthesis of active oestrogens worsens prognosis. Oestrogen metabolising enzymes include steroid sulphatase (STS), which desulphates oestrogens into their active forms, and 17β-hydroxysteroid dehydrogenases (17βHSD), which are estrogen oxidoreductase enzymes. We have previously shown STS activity is increased in human CRC compared to matched-normal tissue. However, the impact of this increased oestrogen de-sulphation on CRC proliferation is unknown. Furthermore, the expression and activity of 17βHSD-1, 17βHSD-7 and 17βHSD-12, all of which reduce the less active oestrone (E_1) to the more potent oestradiol (E_2), have not been fully examined in CRC. Thus, this project investigated the proliferative effects of E_1 and E_2 treatment and overexpression of STS in CRC cell lines. Additionally, how these cell lines metabolised oestrogen was analysed using a novel uPLC-MS/MS technique. Protein and mRNA expression of 17βHSDs capable of reducing E_1–E_2 were examined in human CRC tissue and cell lines. Oestrogen (E_1 and E_2) and STS overexpression increased proliferation of the CRC cell line HCT116. Proliferation also increased in response to G1, a G-protein-coupled estrogen receptor 1 (GPER) agonist. LC-MS/MS indicated HCT116 cells reduced E_1–E_2 most likely catalysed by 17βHSD-12. In human CRC 17βHSD-1 was not expressed, however 17βHSD-7 and -12 expression was significantly elevated ($P<0.0005$) compared to matched normal tissue. GPER was also found to be expressed in the colon. Together these findings suggest the majority of human CRC escalate intratumoural E_2 concentrations through STS and 17βHSD-12. This local oestrogen rise likely acts through GPER to augment tumour proliferation. Therefore, STS, 17BHSD-12 and GPER inhibitors may benefit many CRC patients.

Disclosure

Medical Research Council UK PhD Studentship. Society for Endocrinology Early Career Award.

DOI: 10.1530/endoabs.37.EP1126

EP1127

Expression of ghrelin and somatostatin systems components in pancreatic neuroendocrine tumours and their relationship with clinical-histological characteristics

Aura D Herrera-Martínez[1], Manuel Gahete[2], Rafael Sánchez-Sánchez[3], Teresa Caro Cuenca[3], Raquel Serrano Blanch[4], Raúl Luque[2], María A Gálvez Moreno[1] & Justo Castaño[2]

[1]Department of Endocrinology and Nutrition, Hospital Universitario Reina Sofía, Cordoba, Spain; [2]Department of Cell Biology, Physiology and Immunology, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Hospital Universitario Reina Sofía, University of Córdoba, Campus de Excele, Cordoba, Spain; [3]Department of Pathology, Hospital Universitario Reina Sofía, Cordoba, Spain; [4]Department of Medical Oncology, Hospital Universitario Reina Sofía, Cordoba, Spain.

Pancreatic neuroendocrine tumors (PNETs) are uncommon neoplasms from the endocrine pancreas, whose incidence is recently rising. Unfortunately, an advanced stage is often found at diagnosis; thus, identification of new molecular diagnostic, prognostic, and therapeutic markers is required. Ghrelin and somatostatin/cortistatin systems are two multifunctional regulatory complexes widely distributed throughout multiple tissues, including the pancreas, where they exert diverse (patho)physiological actions; and alterations in these systems can be associated to development/progression of various cancers. Here, we aim to evaluate expression levels of ghrelin and somatostatin systems components in PNETs and explore their putative relationship with histological/clinical patient features. Namely, an observational retrospective study with 28 PNET patients was performed by collecting clinical/histological characteristics and measuring expression levels of ghrelin and somatostatin/cortistatin systems components, by quantitative-PCR, in formalin-fixed paraffin-embedded PNET samples ($n=25$; 52.2% G2, 43.5% G1 and 4.3% G3) and in control adjacent non-tumoral tissues. Mean age was 55±14 years (57.1% females); 21.1% of cases were diagnosed incidentally, 42.1% were functioning tumors and 40.7% had metastasis at diagnosis. Tumour diameter associated negatively to vascular invasion ($P<0.05$) and necrosis ($P<0.05$). Somatostatin receptor (sst) subtypes-1 and -2, cortistatin and ghrelin O-acil-transferase enzyme were overexpressed in PNETs compared to control-tissues ($P<0.01$). Presence of skin lesions at diagnosis was correlated to sst3 expression ($P<0.05$). sst1 expression was negatively associated with vascular invasion ($P<0.05$). Ghrelin-receptor was negatively associated with nerve invasion ($P<0.01$). Mortality was associated to metastasis ($P<0.05$), relapsed disease ($P<0.05$) and somatostatin expression. Interestingly, there was a trend for mortality and sst3 expression to be associated ($P=0.08$). Our results indicate that the majority of ghrelin and somatostatin systems components are expressed in PNETs, where some of these components

display specific associations with clinical-histological parameters, which may help to better understand PNETs pathophysiology and to identify novel molecular targets with potential prognostic and/or therapeutic value for PNETs patients.

DOI: 10.1530/endoabs.37.EP1127

EP1128

A unique case of hyperparathyroidism-jaw tumour syndrome due to a previously unreported pathogenic duplication mutation of CDC73 gene

Pawel Bogusz[1], Elizabeth Mae McConnell[2], Vivienne McConnell[3] & Marian Korda[4]
[1]Registrar in Diabetes and Endocrinology, Craigavon Area Hospital, Craigavon, Co Armagh, UK; [2]Consultant Endocinologist, Craigavon Area Hospital, Craigavon, Co Armagh, UK; [3]Consultant in Genetic Medicine, Belfast City Hospital, Belfast, CoAntrim, UK; [4]Consultant ENT Surgeon, Craigavon Area Hospital, Craigavon, Co Armagh, UK.

Hyperparathyroidism-jaw tumour syndrome (HPT-JT) is a rare autosomal dominant condition characterized by primary hyperparathyroidism (<90%) as a result of parathyroid adenoma or carcinoma (10–15%), ossifying fibromas of mandible and maxilla (30–40%), renal lesions (20%) most commonly cysts and benign and malignant uterine tumours and caused by germline CDC73 pathogenic gene mutations. Currently only 200 cases reported in medical literature. His management has proved more difficult which may be associated with this novel CDC73 pathogenic gene mutation. A 31-year-old man presented with polydipsia, fatigue, corrected calcium of 4.3 and PTH 147. USS and CT neck revealed a left inferior parathyroid adenoma, confirmed by exploration. Histology showed disruption of the capsule with fibrous tissue extending into the lesion at one pole although no overt malignancy. A few months later he had recurrence of symptoms, further hypercalcaemia and a right inferior parathyroid adenoma was excised. Genetic testing detected a novel pathogenic duplication mutation of CDC73 gene leading to premature termination of translation. He presented a third time with hypercalcaemia. No adenoma was identified on imaging however he declined selective venous PTH sampling. His case was extensively discussed with multiple specialists with differing opinions as to total parathyroidectomy +/− auto transplantation. Patient elected for total parathyroidectomy and no auto transplantation due to his germline CDC73 pathogenic gene mutation and 10–15% risk of parathyroid carcinoma development. This unique case illustrates consideration of genetic testing in primary hyperparathyroidism under 45 years, with challenges in rarity and management including implications for biopsy and surgical intervention, multisystem lifelong screening of proband and relatives which is recommended from 5 to 10 years and availability of predictive genetic testing for the familial CDC73 gene mutation. This indicates a significantly more complex case where previous literature has been unable to guide on management and may help advise other endocrinologists.

DOI: 10.1530/endoabs.37.EP1128

EP1129

Extremes in hyperparathyroidism: management of parathyroid carcinoma

Lidia Radomir[2], Daniel Mihai[2], Simona Jercalau[2] & Corin Badiu[1,2]
[1]'Carol Davila' University of Medicine and Pharmacy, Bucharest, Romania; [2]'C.I.Parhon' National Institute of Endocrinology, Bucharest, Romania.

Background
Parathyroid carcinoma (PC) is a rare cause of primary hyperparathyroidism (PHPT), accounting for <1%, with an equal gender distribution and an average age of diagnosis in the fifth decade of life. The diagnosis of PHPT is based on the laboratory finding of high levels of immunoreactive PTH in the presence of severe hypercalcaemia. The only potentially curative treatment for PC is surgery. Early surgery is the most important factor for optimal outcome.

Methods
This case series is based on a multidisciplinary review of four patients with parathyroid cancer, describing their therapeutic management and follow-up. Imagistic evaluation was performed by ultrasound (US), computed tomography scan (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and Technetium-99m sestamibi scintigraphy, for detecting the primary tumour, its local extent and remote metastases.
Results
Between 2008 and 2014 four patients were diagnosed with PC in our clinical department, three men and a woman, with a mean age of 50 years ± S.D. 13.22 (range 38–68). None had family history of hyperparathyroidism or hormonal disorders suggesting multiple endocrine neoplasia. All had severe hypercalcaemia (15.3–19.4 mg/dl) and elevated PTH levels ranging from 15 to 45 times above normal value. Tumor size ranged from 3.2 to 7 cm; two of them had thyroid gland invasion and one thymic invasion. Three patients underwent parathyroidectomy with hemithyroidectomy and one underwent parathyroidectomy with thymectomy and cervical dissection. Schulte stage at diagnosis was between II and IV, while all were classified as high risk. Conformational radiotherapy of the tumor bed was used in two cases. Cinacalcet treatment was tried in one case and chemotherapy regimen in another, without significant improvement. Three patients had local recurrence and the time from the initial surgery to recurrence ranged from 1 month to 1 year.
Conclusion
Parathyroid carcinomas are rare endocrine cancers, with high relapse rate and poor prognosis. Multidiscplinary approach requires detailed imaging, skilled surgeons, endocrinologist and oncologist.

DOI: 10.1530/endoabs.37.EP1129

EP1130

PATZ1 downregulation promotes proliferation and migration in Ras-driven thyroid transformation

Michela Vitiello[1], Teresa Valentino[1], Marta De Menna[2], Paola Francesca[1], Gabriella De Vita[2] & Monica Fedele[1]
[1]Institute of Experimental Endocrinology and Oncology – CNR, Naples, Italy; [2]Department of Molecular Medicine and Medical Biotechnology – DMMBM, Naples, Italy.

Thyroid cancer is one of the most frequent malignancies of the endocrine system, and its incidence is predicted to become the fourth leading cancer diagnosis by 2030. Among thyroid carcinomas, anaplastic thyroid cancer (ATC) is the most aggressive and lethal tumor, which grows very rapidly, invades adjacent tissues and metastasizes, causing death in 1 year from diagnosis. We recently showed that in thyroid cancer PATZ1 expression is downregulated compared to normal thyroid and is further downregulated in follicular (FTC), poorly differentiated (PDTC) and ATC compared to the papillary (PTC) histotype, suggesting PATZ1 downregulation may be involved in late steps of thyroid tumor progression. Consistently, restoration of PATZ1 expression in thyroid cancer cell lines inhibited cellular migration *in vitro* and partially reverted the epithelial–mesenchymal transition *in vivo*. In order to investigate the upstream signaling causing PATZ1 downregulation during thyroid transformation we previously employed an inducible cellular system, in which the oncogenic Ras^{V12} could be induced by tamoxifen in FRTL-5 rat thyroid cells, causing complete malignant transformation towards an undifferentiated phenotype. In this cell system, as well as in FRTL-5 cells stably expressing the Ras^{V12} oncogene, we identified miR-29b as a miRNA specifically upregulated, which targets and downregulates PATZ1 expression downstream of Ras. This is consistent with previous studies showing that in PTC, where PATZ1 is less downregulated, Ras mutations are hardly detected, while in FTC, PDTC and ATC, where PATZ1 is more strongly downregulated, mutations in Ras genes are more frequently found. Here we identify a fundamental role for downregulation of PATZ1 in driving rat thyroid cell transformation by oncogenic Ras. Indeed, PATZ1 overexpression inhibits proliferation and migration of Ras-transformed cells, suggesting that its downregulation is required for Ras-induced thyroid carcinogenesis. Overall, our work demonstrated that PATZ1 is a pivotal regulator acting downstream of miR29b to suppress thyroid cell transformation driven by oncogenic Ras, highlighting a new potential therapeutic target to fight highly malignant thyroid cancer.

DOI: 10.1530/endoabs.37.EP1130

EP1131

Inhibitor of apoptosis protein livin/BIRC7 in adrenocortical tumours

Barbara Altieri[1,2], Silviu Sbiera[1], Silvia Della Casa[2], Sonja Steinhauer[1], Vanessa Wild[3], Guido Fadda[4], Michaela Bekteshi[1], Andreas Rosenwald[3], Alfredo Pontecorvi[2], Martin Fassnacht[1], Bruno Allolio[1] & Cristina L Ronchi[1]
[1]Endocrine and Diabetes Unit, Department of Internal Medicine I, University Hospital of Wuerzburg, Wuerzburg, Germany; [2]Division of Endocrinology and Metabolic Diseases, Institute of Medical Pathology, Catholic University, Rome, Italy; [3]Department of Pathology, University of Wuerzburg, Wuerzburg, Germany; [4]Division of Anatomic Pathology and Histology, Catholic University, Rome, Italy.

Introduction
Adrenocortical tumours comprise frequent adenomas (ACA) and rare highly malignant carcinoma (ACC). Livin/ML-IAP/BIRC7 is a member of the inhibitors of apoptosis proteins family, which are involved in tumorigenesis, mostly through the inhibition of caspase-3. Aim of the study was to evaluate the expression of livin/BIRC7 in normal and neoplastic adrenal glands.
Methods
The mRNA expression of *BIRC7,* its isoforms *livin α* and *livin β,* and *caspase-3* was evaluated by qRT-PCR in 84 fresh-frozen tissues (34 ACC, 25 ACA, 25 normal adrenal glands=NAG), including 19 paired samples of tumour and surrounding NAG. Additionally, livin protein expression was assessed by western blot analysis (WB) in 14 paired samples (eight ACA, six ACC) and by immunohistochemistry in 127 paraffin-embedded tissue sections (67 ACC, 45 ACA, 15 NAG). The relationship with several histopathological and clinical data was also evaluated.
Results
BIRC7 mRNA expression was similar between ACAs (0.01 ± 0.01) and NAG (0.01 ± 0.02), but significantly higher in ACCs (0.06 ± 0.12, $P<0.005$ vs both ACA and NAG), the isoform β was more expressed than α in all the subgroups. Comparable results were obtained with WB. The *caspase-3* was higher in ACA (0.024 ± 0.012) than in ACC (0.017 ± 0.011, $P=0.05$) and NAG (0.018 ± 0.011, $P=0.03$). Livin cytoplasmatic immunostaining was relatively homogeneous (79.5% of more than 50% positive cells). Livin protein expression was higher in ACC than ACA and NAG (mean ± S.D. H-score: 1.72 ± 0.7 vs 1.58 ± 0.5 vs 1.33 ± 0.6, respectively; $P=0.09$), being even higher in ACC samples coming from first surgery ($n=53$, 1.8 ± 0.7) than in those coming from recurrence ($n=8$, 1.25 ± 0.5) or distant metastasis ($n=6$, 1.5 ± 0.5) ($P=0.0001$). No significant correlation was observed with the histopathological and clinical data, including overall survival.
Conclusion
Our study demonstrates that livin/BIRC7 is specifically over-expressed in ACCs, suggesting that it may be involved in adrenocortical tumorigenesis. BIRC7 could represent a novel marker for malignancy and a potential target for therapeutic approaches in ACC.

DOI: 10.1530/endoabs.37.EP1131

EP1132

High-dose treatment with somatostatin analogues in neuroendocrine tumours

Roberta Modica[1], Valeria Ramundo[1], Francesca Marciello[1], Vincenzo Marotta[1], Genoveffa Pizza[1], Anna Chiara Carratù[1], Chiara de Luca di Roseto[1], Pasqualina Buonomano[1], Carla Giordano[2], Francesco Trimarchi[3], Annamaria Colao[1] & Antongiulio Faggiano[1]
[1]Department of Clinical Medicine and Surgery, Section of Endocrinology, Federico II University, Napoli, Italy; [2]Department of Internal and Specialistic Medicine, Endocrinology, University, Palermo, Italy; [3]Department of Clinical and Sperimental Medicine, Endocrinology, University, Messina, Italy.

Somatostatin analogs (SSA) effectively control symptoms in neuroendocrine tumours (NET), besides showing antiproliferative activity. In progressive or metastatic NET, increasing SSA dose or shortening the dosing interval are common clinical practice, though empirical. Aim of this study is to evaluate efficacy and safety of high-dose SSA treatment in patients with progressive disease under standard SSA dose. Twenty-one patients (median age 56.8 years) with NET of different origin were retrospectively identified among 118 patients under SSA therapy. All 21 patients were treated with SSA high dose schedule treatment, after disease progression under standard dose. The median follow-up was 22.3 months (range 4–76). High dose schedule included octreotide LAR in 15 patients (73%) and lanreotide Autogel in 6 (27%). Progression free survival was significantly higher with high-dose treatment compared with standard dose (32 vs 8 months, $P<0.05$). Partial objective tumour response was recorded in one patient (5%), stabilisation in 10 (47.5%) and progression in 10 (47.5%). Among 16 patients who were symptomatic under standard dose, complete clinical response was obtained in 1 (6%), partial response in 9 (57%). Side effects were abdominal discomfort (5%), asymptomatic gallstones (5%) and type 2 diabetes mellitus (5%). High-dose SSA treatment in progressive NET is still effective in patients refractory to standard SSA doses. No additional toxicity is observed compared with standard dose.

DOI: 10.1530/endoabs.37.EP1132

EP1133

Craniopharyngioma audit, single centre experience

Jehangir Abbas, Philip Kane & Vijayaraman Arutchelvan
The James Cook University Hospital, Middlesbrough, UK.

Objectives
Craniopharyngioma is a benign tumour of the suprasellar region that is associated with increased morbidity and mortality in comparison to other causes of hypopituitarism. We aimed to establish the mode of presentation, investigations, treatment outcomes, mortality and subjective improvement in patients with craniopharyngioma in a single institution over 10 years.
Design
Retrospective case notes review of patients with Craniopharyngioma on endocrine register between 2000 and 2010. Clinical records of eligible patients were reviewed and information regarding clinical presentation, medical and surgical management and post treatment outcomes were extracted and collated.
Results
Symptoms at presentation: the commonest presenting symptoms were headache (79%) and visual impairment (75%). Other symptoms were vomiting (27%), cognitive dysfunction (3.4%), weight gain (34.4%), reduced conscious level (3.4%), poor energy level (68.9%), somnolence (13.7%), loss of libido (13%) and polyuria (13.7%).
Surgical outcomes
Gross total resection was achieved in 41.3% but was curative in only 20%. The remaining 80% required further surgical and/or radio therapeutic intervention. Reduction in tumour size was achieved in 86% of patients. CSF leak was 18% post surgical intervention. Visual field were fully recovered in only 27.8% and partially recovered in 26% of patients after surgery and radiotherapy. Endocrine out comes: multiple pituitary hormone deficiency evolved in all patients over time, the commonest were hypothyroidism (79%) and ACTH deficiency (72%). Other deficiencies were gonadotrophins (45%), diabetes insipidus (41%), and GH def (14%). Although neurocoagnitive, psychological and behavioural problems were noted for some patients, only 20% of patients were formally assessed.
Subjective improvement in condition
It was assessed by follow up clinic letters that 59% patients have reported improvement in their condition but 18% of these patients got worse after intervention.
Mortality
All cause mortality was 31%. Tumour related mortality was 25%.
Conclusions
Craniopharyngioma is associated with significant long-term morbidity. Attention to an integrated care pathway that includes standardised neurocognitive and psychological and behavioural assessment would facilitate early appropriate intervention and support leading to an improved quality of life of patients with craniopharygioma.

DOI: 10.1530/endoabs.37.EP1133

EP1134

Gonadotropin releasing hormone antagonist treatment induces cell cycle arrest in gonadal somatic cell and adrenocortical tumours

Milena Doroszko[1], Marcin Chrusciel[1], Ilpo Huhtaniemi[1,3], Jorma Toppari[1,2] & Nafis Rahman[1,4]
[1]Department of Physiology, Institute of Biomedicine, University of Turku, Turku, Finland; [2]Department of Pediatrics, University of Turku and Turku University Hospital, Turku, Finland; [3]Department of Surgery and Cancer, Imperial College London, Faculty of Medicine, London, UK; [4]Department of Reproduction and Gynecological Endocrinology, Medical University of Bialystok, Bialystok, Poland.

We have earlier shown that treatment with gonadotropin releasing hormone antagonist blocked adrenocortical tumour progression through gonadotropin suppression in inhibin α/SV40 T-antigen (inhα/Tag) transgenic (TG) mice. Hereby, we investigated the molecular mechanisms underlying the GnRH antagonist (Cetrorelix acetate; GnRH-a) treatment induced potential antitumor effects on gonadal somatic cell and adrenocortical tumors *in vivo* and *in vitro*. *In vitro* treatment with 10 μM GnRH-a significantly decreased cell viability and proliferation of murine KK1 (granulosa cell), BLT1 (Leydig cell), Cα1 (adrenocortical), all three lines originating from inhα/Tag mice tumors, compared to respective non-treated controls. Flow cytometric analysis revealed a cell cycle arrest at G1 phase in all treated cell lines. We treated *in vivo* 6-mo-old inhα/Tag mice bearing gonadal or 6.5-mo-old mice bearing adrenal tumors for 21 days, with either 3 mg/kg b.w./48 h i.p. of GnRH-a or vehicle. Treatments revealed a significant reduction of tumor burden in all types of tumours with GnRH-a treatment vs vehicle treated group. Our results suggest that GnRH-a treatment, besides blocking the release of gonadotropins, may also directly induce tumour cell death.

Disclosure
Singrid Juselius Foundation
Academy of Finland

DOI: 10.1530/endoabs.37.EP1134

EP1135

Genotype-phenotype correlations in a series of patients with von Hippel-Lindau disease in one single tertiary centre

Raluca Maria Furnica, Nicolas Janin & Dominique Maiter
Cliniques Universitaires Saint-Luc, Brussels, Belgium.

Background
Von Hippel-Lindau (VHL) disease is an autosomal dominant inherited tumour syndrome with an important phenotypic variability. Genetic testing for VHL is simple and accurate.
Objective
In this study, we investigated the relationships between genotype and phenotype in a series of patients with different VHL gene mutations.
Method
This was a retrospective analysis of the clinical and molecular characteristics of 15 VHL patients followed between 1965 and 2012 at the Cliniques Universitaires Saint-Luc. Patients were divided into two groups in order to investigate possible differences in tumour risk and age of onset. Group 1 included six patients with missense mutations, while group 2 comprised nine patients with nonsense mutations ($n=7$), gene deletion ($n=1$) or gene insertion ($n=1$).
Results
The mean age at onset of symptoms was 20.6 ± 9.1 years. Retinal (27%) and CNS haemangioblastomas (27%) were the most frequent initial presentations. In three cases (20%), the initial presentation was a phaeochromocytoma. The cumulative occurrence was 93% for cerebellar haemangiomas (mean age 28.7 years), 67% for retinal haemangiomas (mean age 25.8 years), 47% for renal cancer (mean age 38.2 years), 53% for phaeomochromocytoma (mean age 27.1 years), 53% for multiple pancreatic cysts (mean age 31.8 years) and 33% for pancreatic neuroendocrine tumours (mean age 34.8 years). Eleven different VHL mutations were found: nine mutations in unrelated VHL patients and two mutations in two different kindreds. Patients from group 1 tended to have more frequently a phaeochromocytoma (4/6, 66,7%) than patients from group 2 (4/9, 44,4%), while patients from group 2 tended to have more frequently a endolymphatic sac tumour (3/9, 33,3%) than patients from group 1 (0/6). When we compared prevalence and age of onset of the other types of tumours, we did not find significant differences between the two groups.
Conclusions
In our study there was no significant difference in the phenotype of patients with missense vs nonsense gene alterations.

DOI: 10.1530/endoabs.37.EP1135

EP1136

Clinical characteristics and survival of patients with adrenocortical carcinoma: a single centre experience

Valentina Elezovic, Djuro Macut, Milan Petakov, Sanja Ognjanovic, Tatjana Isailovic, Bojana Popovic, Ivana Bozic Antic, Tamara Bogavac, Dusan Ilic & Svetozar Damjanovic
Clinic of Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia, Belgrade, Serbia.

Adrenocortical carcinoma (ACC) is rare malignancy associated with limited treatment options and poor prognosis. The aim of this study is to review clinical characteristics and survival of patients with ACC in single centre. We retrospectively analysed 60 patients (37 female and 23 males) with pathologically confirmed ACC who were treated at our institution between January 2005 and December 2014. Staging was performed according to European Network Study of Adrenal Tumours (ENS@T) criteria. The median age at diagnosis was 49.0 years (range 14–74), mean tumour size was 11.3 cm (range 3.1–30 cm) and median follow up duration was 34 month (range 3–179). Patients with hormone secreting ACC (43%) mainly presented with isolated Cushing's (20%), or combined with hyperandrogenism (18%) and 57% of patients had non-functioning tumour. The series included 47% low-stage tumours (three stage I, 25 stage II) and 50% high-stage tumours (no stage III, 30 stage IV). At the time of diagnosis 33% of patients had metastasis. Surgical resection was performed in 90% of patients (73% had adrenalectomy, 15% tumour debulking). At 34 patients the median Weiss score was 6 (range 3–8); proliferation index Ki67 index $>10\%$ was in 20/27 patients (median 23.5%, range 2–65%). Up to January 2012 all patients received adjuvant mitotane treatment after surgical resection, and after that date only those with potential residual disease (R1/Rx resection) or with Ki-67 $>10\%$. Since august 2013, plasma mitotane and metabolites levels were measured regularly using HPLC in our institution. Twenty four percent of patients received chemotherapy (EDP 80%, EP 10%, 5FU-DTC-ADM 10%). Median overall survival was 106 months (95%CI 17–194) with 5 year overall survival 53% (76% in stage II, 33% in stage IV). Median disease free survival was estimated 14 months (95%CI 8–20). We presented the overall survival of ACC patients in Serbia, our 10 years' experience.

DOI: 10.1530/endoabs.37.EP1136

EP1137

Effects of cyberknife radiotherapy treatment of pituitary adenomas

Soraya Puglisi[1], Oana Ruxandra Cotta[1], Alfredo Conti[2], Antonio Pontoriero[3], Erika Messina[1], Adriana Albani[1], Francesco Ferrau[1], Marta Ragonese[1], Maria Luisa Torre[1], Flavio Angileri[2] & Salvatore Cannavo[1]
[1]Department of Clinical and Experimental Medicine – Endocrinology, University of Messina, Messina, ME, Sicily, Italy; [2]Department of Neurosciences – Neurosurgery, University of Messina, Messina, ME, Sicily, Italy; [3]Department of Imaging and Biomorphological Sciences – Radiotherapy, University of Messina, Messina, ME, Sicily, Italy.

Introduction
CyberKnife (CK) is an emerging treatment for pituitary tumours (PT) resistant to other therapies.
Patients and methods
We report long-term CK effect on endocrine function and tumour volume in 20 PT patients (11M/10F, mean age 58.6 ± 14.4years). Twelve patients harboured a non functioning adenoma, 2 an ACTH, 5 a GH (one case of TSH co-secretion) and 2 a PRL-secreting PT. Before CK nine patients had normal while 11 presented impaired pituitary function. CK was used as first line treatment in three cases. The mean follow-up period was 21.16 ± 16.35 months (range, 2–90 months).
Results
MRI demonstrated tumour shrinkage in 50% of patients. Tumour increase was evident only in two cases. Pituitary function impairment occurred in three of the nine patients with previous normal pituitary function who developed isolated deficiency in two cases and multiple deficiencies in 1. Among six patients with previously multiple or isolated hypopituitarism, two became panhypopituitary and one developed a new deficit.
Conclusions
CK treatment for PT is safe and effective, ceasing tumour growth in 90%, and inducing tumour shrinkage in 50% of cases. Nevertheless, impairment of pituitary secretion was demonstrated in 30% of cases with previously intact pituitary function and in 50% of already hypopituitary patients.

DOI: 10.1530/endoabs.37.EP1137

EP1138

Real-time shear wave elastography in the evaluation of parathyroid adenomas

Mihaela Vlad, Ioana Golu, Daniela Amzar, Melania Balas, Ioana Zosin & Ioan Sporea
Victor Babes University of Medicine and Pharmacy, Tmisoara, Romania.

Real-time shear wave ultrasound elastography (SWE) is a new technique, which evaluates elasticity and stiffness of the different structure.
Aim
To determine the values of the elasticity index (EI) measured by SWE in parathyroid gland adenomas and to compare with those of normal thyroid tissue.
Subjects and methods
We studied 50 cases (F/M = 42/8), ten with primary or tertiary hyperparathyroidism, diagnosed by specific tests, and 40 healthy volunteers. In all the patients with hyperparathyroidism, parathyroid adenomas were detected by using ultrasound and at least another imaging technique. In six cases surgical removal of parathyroid adenomas was performed and the pathological results confirm the diagnosis. For each parathyroid lesion two or three elastographic determinations were performed and a mean value was calculated and expressed in kilopascals (kPa). In healthy volunteers, thyroid parenchyma was evaluated, by performing three elastographic determinations for each thyroid lobe. A mean value was calculated and expressed in kPa. All the measurements were performed with an Aixplorer system (Supersonic Image, Inc. France), using a linear high-resolution transducer 15–4 MHz.
Results
In ten patients with primary or tertiary hyperparathyroidism, 11 parathyroid adenomas were evaluated by SWE. The mean EI for parathyroid lesions was 9.2 ± 4.8 kPa (4.2–18.2). In healthy volunteers the mean EI was similar in the right and left thyroid 19.9 ± 6.6 kPa vs 19.3 ± 6.6 kPa, $P = 0.69$, respectively. The statistical analysis indicates that the mean EI assessed by SWE in parathyroid adenomas was significantly lower than in nearby normal thyroid parenchyma: 9.2 ± 4.8 kPa vs 19.6 ± 6.2 kPa, $P < 0.0001$.
Conclusion
This new technique can evaluate the EI of parathyroid adenomas, which was significantly lower than EI of normal thyroid parenchyma. This preliminary study indicates that the determination of EI by SWE might be a new method that can help in preoperative localisation of parathyroid adenomas.

DOI: 10.1530/endoabs.37.EP1138

EP1139

Neuroendocrine tumor European patient experience: results from the first global NET patient survey – a collaboration between the International Neuroendocrine Cancer Alliance and Novartis

Kjell Öberg[1], John Leyden[2], Grace Goldstein[3], Maia Sissons[4] & Teodora Kolarova[5]
[1]Uppsala University Hospital, Uppsala, Sweden; [2]The Unicorn Foundation, Mosman, New South Wales, Australia; [3]The Carcinoid Cancer Foundation, Inc., White Plains, New York, USA; [4]NET Patient Foundation, Hockley Heath, UK; [5]APOZ and Friends, Sofia, Bulgaria.

Background
NETs are a rare heterogeneous group of malignancies, often with a delayed diagnosis. Although diagnosis of NETs is increasing (due in part to greater awareness), little has been published on the NET patient experience. We present data on the EU NET patient perspective.
Methods
In 2014, 1928 NET patients from >12 countries, including EU ($n = 763$: Belgium, Bulgaria, France, Germany, Norway, UK, other EU countries (not specified by respondents)), participated in a survey on the NET patient experience conducted by Hall & Partners on behalf of INCA/Novartis and funded by Novartis. Comparisons were significant at $P < 0.05$.
Results
EU patient-reported NET types included gastrointestinal/pancreatic (GI/pNETs, 53%/27%), lung/thymus (11%), and other/unknown (13%). Most patients reported G1/G2 (67%) functional disease (44%); GI NETs were more likely than pNETs to be low grade (G1: 50% vs 32%) and functional (58% vs 23%). 63% of NETs had metastasized at diagnosis (significantly greater for GI/pNETs (71%/62%) than lung NETs (37%)). 41% reported fair/poor health, and 72% said NETs had a negative impact on their lives, including overall energy levels (70%) and emotional health (60%). Having NETs made patients feel anxious/worried (46%) and concerned (44%). Patients made numerous lifestyle adjustments, including dietary changes (GI/pNET, 54%/55%; lung NET, 34%) and increased travel (47%)/related spending (41%) for medical appointments. 87% of respondents not working ($n = 163$) stopped due to NETs; 30% of retirees ($n = 295$) had to stop working earlier than planned. Patients felt well supported by their medical team, particularly endocrinologists (78%), nuclear medicine specialists (75%), and oncologists/nurses (74%/74%). Patients believed more awareness of NETs (38%), information regarding how to manage disease/treatment-related symptoms (37%/33%), and increased access to NET-specific treatments/medical teams (37%/36%) would help them live better with NETs.
Conclusion
This large global NET patient survey demonstrated a substantial impact of NETs on EU patients and identified areas for improvement.
Disclosure
The Global NET Patient Survey was conducted as a collaboration between the International Neuroendocrine Cancer Alliance (INCA) and Novartis Pharmaceuticals. Funding for this survey was provided by Novartis.

DOI: 10.1530/endoabs.37.EP1139

EP1140

Vitamin D receptor and progesterone receptor expression in papillary thyroid carcinoma

Maria Yavropoulou[1], Gregory Panayotou[3], Konstantina Topouridou[1], Anastasia Panteliadou[1], Georgia Karayannopoulou[2], Thomas Zaraboukas[2], Apostolos Goropoulos[4], John Yovos[1] & Kaliopi Pazaitou[3]
[1]Department of Endocrinology and Diabetes, AHEPA University Hospital, Thessaloniki, Greece; [2]Department of Pathology, School of Medicine Aristotle University of Thessaloniki, Thessaloniki, Greece; [3]Department of Endocrinology and Endocrine Oncology, Theagenion Cancetr Hospital, Thessaloniki, Greece; [4]Department of Endocrine Surgery, St Luke's Hospital, Thessaloniki, Greece.

Background
Vitamin D receptor (VDR) and progesterone receptor (PR) expression have been described before in papillary thyroid carcinoma but data regarding association of this expression with tumour histological characteristics are scarce.
Materials and methods
Formalin-fixed, paraffin-embedded specimens from adult patients with papillary thyroid carcinoma (PTC), who underwent total thyroidectomy from 2009 to September 2012 were retrieved. Data regarding tumour size and aggressiveness were recorded. Real-time quantitative RT-PCR and immunohistochemistry was used to characterise the expression of VDR and PR in thyroid follicular cells of the PTC.
Results
A total of 32 thyroid carcinoma specimens were used in the final analysis. Eighteen cancer specimens (56%) overexpressed VDR and 11 of them ($n = 34\%$) overexpressed PR compared to adjacent normal thyroid tissue. Co-expression of the two receptors was found in seven specimens (22%). Expression of PR but not VDR was significantly associated with the tumour size ($r = 0.645$, $P = 0.007$).
Conclusion
VDR is overexpressed in the majority of patients with papillary thyroid carcinoma, compared to normal thyroid tissue. However, the potential role of this receptor in the histological behaviour of PTC remains to be elucidated. Expression of progesterone receptor may be associated with a less favourable prognosis of this tumour type.

DOI: 10.1530/endoabs.37.EP1140

EP1141

Genotype–phenotype analysis in patients with medullary thyroid carcinoma: a single centre experience

Tatjana Isailovic, Gordana Rodic, Djuro Macut, Milan Petakov, Sanja Ognjanovic, Valentina Elezovic, Bojana Popovic, Ivana Bozic Antic, Tamara Bogavac, Dusan Ilic & Svetozar Damjanovic
Clinic for Endocriology, Diabetes and Metabolic Diseases, Clinical Center of Serbia, Belgrade, Serbia.

Introduction
Medullary thyroid carcinoma (MTC) is a malignant neoplasm derived from the parafollicular cells of the thyroid gland. Approximately 25% of them are caused by germline mutations of the *RET* gene, presenting as a part of FMTC, MEN2A or MEN2B syndrome.
Design of the study
We analysed 213 consecutive patients with MTC (142 females, 71 males, age 6–78, mean 45 years), treated in a single centre from 2004 to 2014. Direct DNA sequencing for detection of mutation in coding region of *RET* exons 5, 8, 10, 11, and 13–16, was performed in all patients.

Results
Mutations in *RET* protooncogene were found in 89 (41.8%) MTC patients (age 3–72, mean 37.7 years) and their 33 unaffected relatives (age 10– 70, mean 40 years), comprising 38 different families. FMTC was diagnosed in 37 (41.6%), MEN2A in 47 (52.8%), MEN2B in 5 (5.6%) of MTC patients. A total of 15 different mutations were found. Cys634Phe, Cys634Arg and Val804Met were the most frequent mutations in MTC patients (21.3, 20, and 19.1%, respectively), but the most predominant one among all analyzed patients was Tyr791Phe (29/122 patients, 23%). However, only 9 (31%) of these patients were diagnosed with MTC. The rest of the patients were asymptomatic, or with different renal and auditory abnormalities. Polymorphisms of the *RET* protooncogene were found in 101 (47.4%) of MTC patients. The type or the number of detected polymorphisms did not influence clinical presentation, calcitonin level, or the outcome of the disease.
Conclusion
A higher prevalence of inherited MTC was found in our group of patients than in other studies. The prevalence of different types of mutations among MTC patients is similar as previously reported. However, in contrast to the European studies, an unusually high prevalence of Tyr791Phe mutation was found among our carriers.

DOI: 10.1530/endoabs.37.EP1141

EP1142

TFF3 and *TIMP3* – the candidate marker genes for differentiation diagnosis of follicular cell-derived thyroid tumours

Karolina H Czarnecka[1], Michał Kusiński[2], Maja Kacprzak[1], Dorota Pastuszak-Lewandoska[1], Monika Migdalska-Sęk[1], Ewa Nawrot[1], Daria Domańska[1], Justyna Kiszałkiewicz[1], Krzysztof Kuzdak[2] & Ewa Brzeziańska-Lasota[1]
[1]Department of Molecular Bases of Medicine, I Chair of Internal Medicine, Medical University of Lodz, Lodz, Poland; [2]Department of Endocrine, General and Vascular Surgery, Chair of Endocrinology, Medical University of Lodz, Lodz, Poland.

The search for new differentiating biomarkers in follicular-cell derived thyroid tumors (FCDT), especially for the FNAB with underdetermined cytology, is an important scientific task. Disturbed expression of tumor suppressor genes plays important role in thyroid carcinogenesis. In this study we focused on epigenetic mechanism influencing on trefoil factor 3 (TFF3) and tissue inhibitor of metalloproteinases 3 (TIMP3) expression.
Aim of the study
Evaluation of *TFF3* and *TIMP3* promoter hypermethylation and gene expression as candidate biomarkers in differentiating diagnosis of FCDT neoplasms.
Material
Thyroid neoplasms and matching macroscopically unchanged tissues (control) from 86 patients with preoperative FNAB diagnosis: 'follicular neoplasm'/PTC. Final diagnosis: FA ($n=9$), PTC ($n=35$), FTC ($n=9$) and NG ($n=33$).
Methods
DNA bisulfite conversion, followed by promoter methylation level evaluation in methylation specific PCR, Methylation Index (MI) calculation. mRNA expression level (RQ) measured by real-time PCR using Low Density Arrays. The results (MI, RQ) were correlated with the clinicopathological features.
Results
TIMP3 MI value correlates with RQ ($P=0.029$) and increase with patients age. *TIMP3* MI and RQ are higher in woman vs men ($P=0.016$). *TIMP3* MI value was significantly higher in follicular lesions (FTC/FA), than in NG and PTC ($P=0.049$). *TIMP3* expression was the highest in FA, the lowest in FTC, RQ values don't correlate with methylation pattern. *TFF3* MI value revealed the opposite correlation to *TIMP3* – low MI in FTC/FA. In PTC *TFF3* MI correlates with RQ level ($P=0.01$). The significant correlations among *TIMP3* and *TFF3* MI levels and among their expressions were observed ($P=0.00008$ for MIs, $P=0.00$ for RQs). In women positive correlation between MIs and RQs for *TIMP3* and *TFF3* were found ($P=0.0004$, $P=0.00$ resp.). RQ values regarding pTNM groups reversely correlate with MI for both genes ($P>0$).
Conclusions
The increased *TIMP3* MI values in FA/FTC, and *TFF3* in PTC suggest that can be regarded as promising biomarkers for FCDT distinguishing. Our research indicates that simultaneous analysis of methylation profile and expression level of *TIMP3* and *TFF3* may be diagnostically useful. Further studies are needed.
Disclosure
This work was financially supported by the Polish Ministry of Science and Higher Education (Iuventus Plus programme, 2012–2015, grant No. 0082/IP1/2011/71).

DOI: 10.1530/endoabs.37.EP1142

EP1143

A case series of etomidate use in ACTH ectopic syndrome in endocrine neoplasms

Georgios Boutzios, Georgios Nikolopoulos, Krystallenia Alexandraki, Maria Kaltsatou, Maria Chrysochoou, Marina Tsoli & Gregory Kaltsas
Endocrine Unit, Department of Pathophysiology, University of Athens, Medical School, Laiko Hospital, Athens, Greece.

Introduction
Etomidate is an imidazole derivative which inhibits several enzymatic steps (11β-hydroxylasey, 17β-hydroxylase, 17,20-lyase, cholesterol side-chain cleavage). Intravenous etomidate at sub-anaesthetic doses remains an important option when i.v. administration is required for rapid treatment of severely ill patients with hypercortisolaemia (Cushing's syndrome, CS) and is almost always very effective.
Case series
A 49-year-old woman with left adrenocortical carcinoma (T4N1M1, stage IV during ENSAT2008, Ki-67: 15%) and CS, relapsed 6 months after surgical removal of the primary tumour while she had received chemotherapy and adrenolytic therapy. Recurrence involved new liver metastases and an increase in cortisol values with recurrence of CS. She received 2.4 mg/h of etomidate intravenously for 7 days; serum cortisol (F) and 24-h urine cortisol concentrations (UFC) decreased (pre-treatment F: 1456.5 μg/dl, post-treatment F: 613.8 μg/dl, pre-treatment UFC: 773.5 mg/24 h, post-treatment UFC: 615 mg/24 h). The patient died because of sepsis one month later. A 72-year-old man with atypical lung neuroendocrine neoplasm (NEN) (T1aNxMx,Ki-67: 4–7%) and ectopic secretion of ACTH (ACTH: 78.7 pg/ml) had surgical removal of the primary tumour followed by chemotherapy and somatostatin analogues. He had disease recurrence 6 years later. He was treated with metyrapone and ketoconazole without adequate control of CS (pre-treatment-UFC: 709 mg/24 h, post-treatment-UFC:416 mg/24 h). Etomidate was administered at a dose of 3–3.3 mg/h intravenously and hypercortisolaemia was controlled (pre-treatment-F: 44 μg/dl, post-treatment-F: 23 μg/dl). A bilateral adrenalectomy was performed to control hypercortisolaemia. A 51-year-old woman with medullary thyroid carcinoma (T3NxM1, stage IV), liver metastases and ectopic secretion of ACTH (ACTH: 153 pg/ml, F: 74 μg/dl) underwent thyroidectomy without resolution of CS. She received etomidate intravenously at a dose of 2.6 mg/h with a decrease in cortisol levels (pre-treatment-F: 273.8 μg/dl, post-treatment-F:79.2 μg/dl). The patient died because of a septic shock 2 days later.
Conclusion
Etomidate may be used as first-line treatment in severely ill patients with CS. However, it needs to be very carefully monitored, because of sedation that may be apparent in higher doses, and adjustments should be made with regards to renal failure and stressed situations such as sepsis.

DOI: 10.1530/endoabs.37.EP1143

EP1144

Differentiated thyroid carcinoma arising from or associated with struma ovarii: a report of two cases

Lavinia Vija[1], Andrei Goldstein[1], Daniela Neamtu[1], Mariana Purice[1], Florin Alexiu[1], Doina Piciu[3] & Corin Badiu[1,2]
[1]Nuclear Medicine Department, 'C.I. Parhon' National Institute of Endocrinology, Bucharest, Romania; [2]'Carol Davila' University of Medicine and Pharmacy, Bucharest, Romania; [3]'Ion Chiricuta' Oncology Institute, Cluj-Napoca, Romania.

Introduction
Struma ovarii is a rare condition which elicited considerable interest because of its many unique features like its relationship to teratoma and differentiated thyroid cancer. The most common thyroid carcinomas to arise in struma ovarii are papillary and follicular.
Objectives
We describe two patients with differentiated thyroid carcinoma originating from malignant struma ovarii.
Results
Our index patient is a 32-year-old woman with well differentiated follicular carcinoma who developed peritoneal dissemination and appendix tumoural infiltration of a follicular variant of papillary thyroid carcinoma arising from an ovarian teratoma. There was no thyroid carcinoma within thyroid tissue (total thyroidectomy). Whole body scintigraphy (WBS) with therapeutic activity of I-131 (two sessions; cumulated activity: 300 mCi) revealed disseminated pulmonary and bone metastases with a complete response after radioiodine therapy. The second patient is a 49-year-old woman presenting with bone pain revealing bone follicular thyroid carcinoma metastases on biopsy; total

thyroidectomy with lymphadenectomy was performed revealing a follicular thyroid carcinoma T3N1bM1. Two years later, ovarectomy revealed a malignant struma ovarii. Surgical spinal decompression and resection of several vertebral metastases as well as seriate adjuvant radioiodine therapy (279 mCi I-131) were performed. WBS revealed high uptake on cervical lymph node and disseminated pulmonary and skeleton metastases justifying the pursue of radioiodine therapy.
Conclusions
Vascular invasion of the thyroid carcinoma within struma ovarii was not identified in any of the cases; however, disseminated metastases were identified. Mechanisms still need to be searched for. At present, treatment for patients with thyroid carcinoma within ovarian malignant struma ovarii comprises resection of the extraovarian tumoral tissue with subsequent thyroidectomy followed by radioactive iodine ablation.

DOI: 10.1530/endoabs.37.EP1144

EP1145

Mitotane treatment for metastatic Leydig cell tumour

Vasileios Chortis[1], Nicholas Johal[1], Michael Cullen[2], Irina Bancos[1], Peter Guest[2], Emilio Porfiri[2] & Wiebke Arlt[1]
[1]Centre for Endocrinology, Diabetes and Metabolism, University of Birmingham, Birmingham, UK; [2]University Hospital Birmingham, Birmingham, UK.

Introduction
Testicular leydig cell tumours (LCTs) are rare stromal tumors often associated with androgen excess. Metastatic malignant LCTs typically show resistance to radiotherapy and cytotoxic chemotherapy, calling for alternative management options. Here we describe our experience with treatment of two patients with metastatic LCTs with the adrenolytic drug Mitotane.
Patients/methods
Case 1: A 51-year-old patient presented with a 6 month history of restlessness, aggressiveness, insomnia, facial plethora and increasing body hair growth, 15 years after successful orchidectomy for malignant LCT. Imaging by computed tomography revealed disseminated metastatic deposits. Biochemical work-up revealed severe androgen excess as the cause of his signs and symptoms, with a plasma testosterone of 93 nmol/l and a 20-fold rise in urinary excretion of active androgen metabolites (androsterone and etiocholanolone), as well as high urinary cortisol. *Case 2:* A 65-year-old patient presented with disseminated disease 3 years after orchidectomy for LCT. This was also associated with steroid hormone excess, including high testosterone (104 nmol/l) and oestradiol. Both patients were commenced on palliative chemotherapy with mitotane.
Results
In both cases, introduction of mitotane led to prompt control of the underlying hormonal excess, with a precipitous decrease in circulating testosterone and oestradiol levels, diminution of the excretion rate of all urinary androgen metabolites and substantial inhibition of the conversion of testosterone to dihydrotestosterone, as demonstrated by serial urine steroid profiling by gas chromatography/mass spectrometry. Clinically, this resulted in a rapid alleviation of the debilitating clinical symptomatology of hyperandrogenism. Radiologically, stabilisation of the rapidly progressive disease was documented on follow-up imaging for 6 months in case 1, while partial response was noted in case 2.
Conclusions
Mitotane can be an effective treatment option for patients with functional metastatic LCTs, offering prompt palliation of the distressing symptoms of hormone excess and, in some cases, disease stabilisation.
Disclosure
This work was supported by the European Union under the 7th Framework Program (FP7/2007–2013, grant agreement 259735, ENSAT-CANCER, to Wiebke Arlt), the WellcomeTrust (Clinical Research Training Fellowship WT101671AIA, to Vasileios Chortis).

DOI: 10.1530/endoabs.37.EP1145

EP1146

Patients with multiple endocrine neoplasia type 1 (MEN1) have late progression and long survival despite the presence of disseminated disease: the experience of a referral centre in Greece

Georgios Boutzios, Krystallenia Alexandraki, Eleftherios Chatzellis, Maria Chrysochoou, Marina Tsoli, Maria Kaltsatou, Georgios Nikolopoulos, Panagiotis Moschouris & Gregory Kaltsas
Endocrine Unit, Department of Pathophysiology, University of Athens, Medical School, Laiko Hospital, Athens, Greece.

Introduction
Multiple endocrine neoplasia type 1 (MEN1) is a genetic disorder involving mainly parathyroid tumours, pancreatic neuroendocrine neoplasms (pNENs) and pituitary tumours. In the present study we have registered demographic, clinical, imaging, pathological characteristics, therapeutic options, response to treatment and overall outcome of patients with MEN1.
Methods/design
35 patients with MEN1 registered in our data base have been studied (14 females, mean age on diagnosis 39 years; range: 15–64), followed during the period 2004–2014. The primary sites, the presence of functional syndrome, and metastatic foci have been registered. TNM system has been used for staging and proliferation index Ki-67 for grading. The therapeutic management and the outcome have been also registered.
Results
24 (68.6%) patients were the index cases. 19 (54.3%) had a positive gene mutation while 5 (14.3%) did not have the mutated gene. 22 (62.9%) patients had a pituitary adenoma and 31 (88.6%) had hyperparathyroidism. All patients but one suffered from pNENs. 11 (32.4%) patients had a functional syndrome. Metastatic liver deposits were found in 6 (17.6%) patients. In the first diagnosis, 21 (61.9%) neoplasms were found in stage 1, 3 (8.5%) in stage 2, 4 (11.9%) in stage 3 and 6 (17.7%) in stage 4. 14 (41.2%) patients had surgical removal of the neoplasms. The other systemic or local therapies that the patients received as monotherapy or in combination as first line treatment are as following: somatostatin analogues ($n=5$), chemotherapy ($n=1$), neoplasm-targeted molecular therapy ($n=1$), radionucleotides ($n=2$), chemoembolization ($n=1$). In the last follow-up of the present analysis 3 (8.6%) patients died of their disease out of the 24 under current follow-up: two with grade 1 pNEN and one grade 2 pNEN.
Conclusion
The present registry implies that the majority of the patients with MEN1 have late progression and long survival despite the presence of disseminated disease, confirming the necessity of specific therapeutic and diagnostic options following the guidelines as well as their management from referral centers under multidisciplinary teams.

DOI: 10.1530/endoabs.37.EP1146

EP1147

Expression of shorter isoforms of retinoblastoma interacting zinc-finger protein in seminoma tissues

Valentina Rossi[1], Caterina De Rosa[2], Ciro Abbondanza[2], Erika Di Zazzo[1,3], Bruno Montcharmont[3] & Antonio Agostino Sinisi[1]
[1]Dpt Scienze Cardiotoraciche e Respiratorie, Second University of Napoli, Napoli, Italy; [2]Dpt Patologia Generale, Second University of Napoli, Napoli, Italy; [3]Dpt Scienze per la Salute, University of Molise, Campobasso, Italy.

The full-length retinoblastoma interacting zinc-finger protein (RIZ), codified by ten exons, has tumour suppressive and differentiating properties and is known to be a downstream effector in classical oestrogen target tissue. In many normal and malignant tissues alternative splicing isoforms, RIZ1 and RIZ2, frame-shift mutations and/or exon deletions have been found, but their oncogenic role is still debated. Although the presence of RIZ1 in the testis has been described, in gonadal tumours the relative expression of two isoforms, the presence of gene product variants has not been investigated yet. Aim of this study was to evaluate RIZ expression in normal and malignant testis. We analysed five seminomas, four non-seminomas and four control testis tissue samples. RNAs were extracted on frozen samples and RIZ expression measured by semi-quantitative and quantitative Real time RT-PCR using RPS28 as housekeeping gene. In order to identify the presence of different length variants, we analysed the transcripts of the head exon1 and of the tail exons 9 and 10.
Results and discussion
RIZ transcript was found in all samples analysed. Moreover, exon 9-transcript levels were higher than C-terminal conventional tail exon 10 level, absent in one seminoma sample. Thus, the balance of head and tail exon transcript levels revealed a greater expression of a shorter RIZ gene isoform in seminomas vs non-seminomas and health testis samples. Our data suggest that shorter RIZ isoforms, prevalent in malignant testes, may exert a potential oncogenic and de-differentiating role in male gonad.
Disclosure
This work was supported by PRIN 2008 (grant number 20085Y7XT5_005 to AAS).

DOI: 10.1530/endoabs.37.EP1147

EP1148

Succinate dehydrogenase B associated bladder paragangliomas

U Srirangalingam[2], A Banerjee[1], E George[3], M Druce[1], M Waterhouse[1], S L Chew[1], J Peters[1], P Patki[1], A J Kumar[1], D Berney[1], A Sahdev[1], W M Drake[1] & S A Akker[1]
[1]St Bartholomew's Hospital, London, UK; [2]Royal Free Hospital, London, UK; [3]Queen Elizabeth Hospital, King's Lynn, UK.

Objective
Succinate dehydrogenase B (SDHB) germline mutations are associated with predominantly extra-adrenal paraganglioma (PGLs) and high rates of metastatic disease. Bladder paragangliomas are a rare form of chromaffin cell tumours arising from the bladder wall. The aim of the study is to highlight the preponderance of bladder paragangliomas associated with SDHB gene mutations.
Design
Retrospective case series.
Patients
Five of eight subjects (62.5%) subjects with bladder paragangliomas found to have SDHB mutations. Subjects were seen at St Bartholomew's and associated hospitals, between 1989 and 2013.
Measurements
Basic demographics, disease characteristics, genetics, clinical outcomes.
Results
Genetic testing confirmed germline SDHB mutations. Median age at first diagnosis was 24 years (range 18–68). 60% of patients presented with micturition related symptoms of catecholamine excess. Plasma and/or 24-h urine catecholamines/metanephrines were raised in 4/5 (80%) subjects. A positive family history was apparent in 2/5 (40%). Surgical resection was undertaken in four subjects and one subject awaits surgery. Histopathological or radiological analysis confirmed extension through the lamina propria in 4/5 (80%) subjects. Distant metastatic disease developed in 2/5 (40%) subjects within 4 years of the initial tumour diagnosis. A non-invasive 5.4 mm bladder paraganglioma was identified and excised at an early stage through the SDHB surveillance program. One subject died from metastatic disease 6 years after the initial diagnosis.
Conclusions
The bladder is a 'hot-spot' for SDHB associated paragangliomas linked with high rates of invasive disease. Intensive surveillance regimes, with a focus on the bladder can allow early identification and treatment of potentially aggressive disease.

DOI: 10.1530/endoabs.37.EP1148

EP1149

Excision of phaeochromocytoma and paraganglioma involving the great vessels

U Srirangalingam[2], K Gunganah[1], L Parvanta[1], K Metcalfe[1], G M Besser[1], A Sahdev[1], H S Flora[1], S Bhattacharya[1], R Carpenter[1], S Akker[1], S J Edmondson[1] & W Drake[1]
[1]St Bartholomew's Hospital, London, UK; [2]Royal Free Hospital, London, UK.

Objective
The aim of the study was to describe the surgical management of phaeochromocytomas and paragangliomas which lie in close proximity to or involve the great vessels including the aorta and vena cava.
Design
Retrospective case-series. Patients: five subjects undergoing surgical excision of either a phaeochromocytoma or paraganglioma involving the great vessels seen at St Bartholomew's Hospital, UK (2004–2013).
Measurements
Clinical presentation, genetic mutations, tumour location, catecholamine secretion, pre-, intra- and post-operative course.
Results
Of the five subjects (age range 16–60 years), three had thoracic paragangliomas located under the arch of the aorta, one had an abdominal paraganglioma in which preoperative imaging was unable to delineate that the tumour was invading the aorta and one had a massive phaeochromocytoma invading the IVC. Three of the four subjects tested had predisposing germline mutations. All subjects had alpha and β adrenergic blockade prior to surgery. The thoracic paragangliomas were excised following cardiopulmonary bypass and aortic transection to access the tumours. The abdominal paraganglioma invading the aorta was resected with part of the aorta to clear disease and required insertion of an aortic Dacron graft. The phaeochromocytoma invading the IVC was resected en bloc with the right kidney with a venotomy to extract to resect the tumour nodule invading the IVC. Only one subject experienced an early post-operative complication, which was managed conservatively, and all subjects made a good recovery from surgery.
Conclusion
Excision of phaeochromocytoma and paraganglioma involving the great vessels is high-risk surgery and should be undertaken in a tertiary referral centre within a multidisciplinary setting. Subjects require comprehensive radiological and biochemical assessment. Meticulous pre-operative preparation and appropriate intra- and post-operative back-up are essential. In some cases radiological imaging is unable to resolve the tumour anatomy and extent pre-operatively and direct visualisation of the tumour may be the only way to clarify the surgical strategy, Pre-operative knowledge of the genetic predisposition may influence surgical management.

DOI: 10.1530/endoabs.37.EP1149

EP1150

A one-stop multi-disciplinary VHL clinic: patient benefits and feedback

S O'Toole[1], L McAndrew[1], W Drake[1] & U Srirangalingam[2]
[1]St Bartholomew's Hospital, London, UK; [2]Royal Free Hospital, London, UK.

Introduction
Von Hippel-Lindau (VHL) syndrome is a complex multi-organ disorder with significant associated morbidity and mortality. Patients see multiple specialities and have many clinic appointments which can significantly disrupt their lives. In 2012 the St Bartholomew's VHL multi-disciplinary clinic was set up. It consists of an amalgamated one-stop clinic for patients and their families when all relevant specialities are seen in one sitting. The major aims were to: i) provide a more cohesive service and maximise patient benefit from appointments; ii) consolidate clinical experience and expertise in the management of VHL.
Methods
Analysis of medical records from 2000 until the present day for all VHL patients cared for at St Bartholomew's Hospital, London. A prospective patient questionnaire was completed by patients attending the clinic.
Results
27 VHL patients (15 male) are under the care of St Bartholomew's Hospital; 18 (66.7%) attend the multi-disciplinary clinic. 21 completed questionnaires were returned. The mean number of hospital attendances per patient per year was 3.34. This was significantly less after the introduction of the multi-disciplinary clinic (3.59 vs 2.50, $P < 0.05$). All but two patients attended hospital less frequently after the introduction of the multi-disciplinary clinic. Patient feedback was positive. All respondents thought a one-stop clinic was a good idea and 95% preferred to be seen at the same time as their family. Recurring comments included the benefits of combined consultations and the time saved. The vital role of the specialist nurse was highlighted. Reported downsides were limited and centred on the organisation of the consultation.
Discussion
An amalgamated one-stop multi-disciplinary VHL clinic is practical and reduces hospital appointments whilst being well received by patients. In addition the physical bringing together of all interested parties (both patient and medical) allows for improved communication and truly shared decision making.

DOI: 10.1530/endoabs.37.EP1150

EP1151

Progesterone is a potent substance which inhibits the migration of ovarian cancer cells by reducing epithelial-mesenchymal transition via progesterone receptor-dependent pathway

So-Ye Jeon & Kyung-Chul Choi
Laboratory of Biochemistry and Immunology, College of Veterinary Medicine, Chungbuk National University, Cheongju, Chungbuk, Republic of Korea.

Ovarian carcinoma (OC) is the most deadly and leading cause of cancer death occurring in the female reproductive tracts. Several factors involved in ovarian carcinoma remain poorly defined and the therapy for OC is limited. Epidemiological data strongly suggest that endogenous and exogenous steroid hormones may play important roles in ovarian carcinogenesis. One of the primary steroid hormones, progesterone (progesterone), offers protection against ovarian carcinogenesis. We predicted that progesterone would inhibit the migration of

BG-1 ovarian cancer cells by reducing epithelial-mesenchymal transition (EMT) as well as the growth of cancer cells. First, we investigated the expression of progesterone receptors in ovarian cancer cells with RT-PCR. Next, we determined a proper concentration of progesterone, 17β-estradiol (E_2; a positive control), and Mifepristone (anti-progesterone receptor agent) through MTT assay. We confirmed that progesterone reduced the ovarian cancer cell viability in a dose-dependent manner, which was inhibited by Mifepristone. Also, the migration of ovarian cancer cells was reduced by the treatment of progesterone in comparison with negative and positive control groups. Additionally, the alteration of EMT markers such as vimentin was examined at mRNA and protein levels by using reverse-transcription (RT)-PCR and western blot. The expression of Vimentin was reduced in the treatment of progesterone while the expression of its reverse transition marker E-cadherin was increased. These results indicate that progesterone can inhibit the migration of BG-1 ovarian cancer cells by reducing EMT. Further studies using *in vivo* xenografted mouse models will be needed to predict that progesterone significantly inhibits the growth of ovarian cancer without any virulent effects on the animals. Consequently, the present results represent that progesterone is a potent substance which inhibits the growth of human ovarian cancer cells and metastasis. Therefore, this hormone therapy may be a clinically effective tool for the treatment of human ovarian cancer. (This work was also supported by a grant from the Next-Generation BioGreen 21 Program (NO. PJ009599), Rural Development Administration, Republic of Korea).

Disclosure

This work was also supported by a grant from the Next-Generation BioGreen 21 Program (NO. PJ009599), Rural Development Administration, Republic of Korea.

DOI: 10.1530/endoabs.37.EP1151

Clinical Cases – Pituitary/Adrenal

EP1152

A case of TSH secreting pituitary adenoma with Evans' syndrome

Toshiro Seki[1], Atsushi Yasuda[1], Natsumi Kitajima[1], Masami Seki[2], Masayuki Oki[1], Atsushi Takagi[1] & Masafumi Fukagawa[1]
[1]Tokai University School of Medicine, Kanagawa, Japan; [2]Seirei Numazu Hospital, Shizuoka, Japan.

Introduction

To the best of our knowledge, there is no case report of Evans' syndrome associated with TSH secreting pituitary adenoma (TSHoma).

Case report

A 30-year-old woman was admitted to near hospital due to purpura and ecchymoses on her limb and body and epistaxis. A hematologic disease was suspected and she was referred to our hospital. The diagnosis of Evans' syndrome was made on the bases of idiopathic thrombocytopenic purpura (ITP) and autoimmune haemolytic anaemia (AIHA). Physical examination showed acromegalic features. She had the history of malocclusion and thyroid gland enlargement 4 years prior to admission. Endocrinological tests suggested syndrome of inappropriate secretion of TSH (SITSH) and magnetic resonance imaging (MRI) of the brain demonstrated a pituitary tumor. An oral 75-g glucose tolerance test revealed impaired glucose tolerance, but GH was not suppressed by high serum glucose. Initial studies suggested that this patient had hyperthyroidism due to TSH secreting pituitary adenoma and the adenoma concomitantly secreted GH.

Conclusions

Recently, several cases of Evans' syndrome associated with hyperthyroidism by autoimmune thyroid disease such as Graves' disease suggest that these two conditions may have a common immunological background. In our case, hyperthyroidism is due to TSHoma. Thus, it is suggested that thyroid hormone excess itself promote autoimmunity in Evans' syndrome The early treatment for hyperthyroidism is necessary in TSHoma because there is the possibility that normalisation of thyroid hormone may prevent the development of Evans' syndrome.

DOI: 10.1530/endoabs.37.EP1152

EP1153

Recurrent hyponatremia in woman with undiagnosed postpartum pituitary insufficiency

Maria Kurowska, Joanna Malicka, Agnieszka Zwolak & Jerzy S Tarach
Department of Endocrinology, Medical University, Lublin, Poland.

Introduction

Hyponatremia occurs in 33–69% of women with postpartum pituitary necrosis. The aim of the study was to present a patient in whom recurrent hyponatremia was one of the dominant symptoms of postpartum anterior pituitary hormones deficiency.

A case report

55-year-old woman with a diagnosis of Sheehan syndrome established 19 years after the last labor complicated by massive bleeding due to uterine atonia. The first symptoms of pituitary insufficiency were the lack of lactation and secondary amenorrhea. In addition, the patient complained of weakness, fatigue, psychomotor retardation, depressed mood, dizziness, hypotension including orthostatic hypotension, flushing, loss of appetite, abdominal pain, recurrent episodes of nausea and vomiting, weight loss. She observed dry skin, loss of pubic and axillary hair, loss of eyelashes and eyebrows and recurrent infections of the urogenital system. Over the last few years she was hospitalised for recurrent hyponatremia (Na 115–125 mmol/l) many times. The hormonal measurements were: ACTH = 32.5 pg/ml; cortisol circadian rhythm = 2.6–1.3 μg/dl; daily urine cortisol excretion = 6 μg/day; DHEAS < 3.0 μg/dl (normal range: 25.9–460.2); PRL = 3.5 ng/ml; LH = 1.5 mIU/ml; FSH = 5.03 mIU/ml; estradiol < 12.0 pg/ml; GH < 0.1 ng/ml; IGF-1 = 10 μg/l (normal range: 50–184); fT_4 = 6.6 pmol/l; fT_3 = 1.1 pmol/l; TSH = 2.36 mIU/l. Ultrasound examination showed the 8.5 ml thyroid gland with normal echogenicity. MRI revealed partial empty sella syndrome with small (7 × 3 mm), symmetric pituitary with normal morphology of the signal.

Conclusion

Recurrent hyponatremia may be one of the dominant symptoms in the patient with long-lasting and unrecognised pituitary insufficiency after a pathological labour.

DOI: 10.1530/endoabs.37.EP1153

EP1154

A case report of Langerhan cells histiocytosis – the need for a good transition care

Ana Margarida Balsa[1], Margarida Bastos[2], Carolina Moreno[2], Daniela Guelho[2], Luís Cardoso[2], Nuno Vicente[2], Diana Martins[2], Diana Oliveira[2], Márcia Alves[1], Joana Guimarães[1] & Francisco Carrilho[2]
[1]Serviço de Endocrinologia, Diabetes e Nutrição do Centro Hospitalar do Baixo Vouga, Aveiro, Portugal; [2]Serviço de Endocrinologia, Diabetes e Metabolismo do Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.

Introduction

Langerhan Cells Histiocytosis (LCH) is a rare heterogeneous idiopathic clinical entity involving clonal proliferation of Langerhan cells that may infiltrate most commonly bone, skin, lymph nodes or lungs. It affects mainly children between 5 and 15 years. The most common endocrine manifestation is diabetes insipida.

Clinical case

The authors describe a case of a 19-year-old female patient, admitted in the Transition Follow-up of the Endocrinology Department of Coimbra's Hospital and Universitary Center. In her past medical history, at the age of 15 months she presented with rash, fever and distended abdomen. Complementary diagnosis exams showed anemia and hepatosplenomegaly and the first bone marrow examination reached the diagnosis of Kala-Azar but the directed treatment did not show clinical improvement. A new bone marrow exam was conducted with a final diagnosis of LCH. After 17 years over the diagnosis, two recurrences and 27 chemotherapy courses she was now referred to Transition Follow-up. On admission she showed no sign of recurrent disease, no anterior-pituitary disfunction, the maintenance of pituitary stalk thickening at MRI and diabetes insipida, treated with desmopressin.

Discussion

Since it affects mostly children, the majority of published literature about HCL concerns pediatric patients. Our patient reached adulthood and now we face the challenge of planning the future follow-up, concerning the risks of recurrence of the primary disease and the consequences and long-term effects of the treatment of a childhood cancer.

DOI: 10.1530/endoabs.37.EP1154

EP1155

Case report: adrenal phaeochromocytoma presenting with ileus, renal vein thrombosis and pulmonary embolism

Ray Lai, Daphne Lee, Huiling Liew, Timothy Peng Lim Quek & Cherng Jye Seow
Department of Endocrinology, Tan Tock Seng Hospital, Singapore, Singapore.

Introduction
We report a patient who presented with presumed intestinal obstruction, and was subsequently diagnosed with an adrenal phaeochromocytoma associated with venous thromboembolism. We review the literature and discuss underlying mechanisms for these uncommon manifestations.
Case presentation
A 56-year-old man with background untreated hypertension presented with abdominal distension, vomiting, breathlessness and haemoptysis. Heart rate (HR) was 126/min and blood pressure (BP) 159/95 mmHg at presentation. CT scan of the abdomen revealed dilatation of a long segment of small bowel, with a transition point at the distal jejunum. A heterogeneous 4.6×4.5×4.9 cm left adrenal mass with associated renal vein thrombosis and left lower lobe segmental pulmonary embolism was noted. Emergent exploratory laparotomy and bowel decompression followed. Intra-operatively, no mechanical cause for intestinal obstruction was identified. Post-operatively, he had uncontrolled hypertension and tachycardia, with BP up to 200/120 mmHg, and HR up to 120–140/min. Urinary catecholamines were ten times above the normal range, confirming the diagnosis of left adrenal phaeochromocytoma. Ga-68 DOTA-TATE PET-CT did not reveal any evidence of metastatic disease. Anticoagulation was started and patient was optimised medically before laparoscopic left adrenalectomy was performed.
Discussion
These uncommon initial manifestations can be explained by a state of catecholamine excess. Ileus occurs due to suppression of gastrointestinal peristalsis. Catecholamines exert a direct effect on primary and secondary haemostasis, and adrenergic infusions have been shown *in vivo* to increase fVIII activity, vWF antigen, tPA activity, and platelet activation and aggregation. Both arterial and venous thromboses have been reported in the literature. Overall, these are relatively uncommon and also likely under-reported phenomena in patients with phaeochromocytoma. A greater awareness of these associations will enable clinicians to avoid missing a potentially catastrophic diagnosis.

DOI: 10.1530/endoabs.37.EP1155

EP1156

Phaeochromocytoma and hypoglycaemic fits: a case report

Ivar Følling[1,2], Anne Lise Olsen[1], Ingrid Nermoen[1,2] & Per Medbøe Thorsby[3]
[1]Department of Endocrinology, Akershus University Hospital, Nordbyhagen, Norway; [2]University of Oslo, Oslo, Norway; [3]Hormone Laboratory, Oslo University Hospital, Oslo, Norway.

Introduction
Phaeochromocytomas often induce hyperglycaemia. Few cases are reported with hypoglycaemic fits. The mechanism is unknown. Our findings may indicate a mechanism.
The patient
A 37 year old female had a phaeochromocytoma, with typical characteristics: attacks of headache, nausea and sweating. High blood pressures, up to 237/134. Electrocardiogram indicated ischemia, normal coronary arteries on dynamic CT, normal Echo-Doppler heart examination. HbA1c 6.6%. Fasting glucose 8.8 mmol/l. Plasma metanephrine and normetanephrine, and 24-h-urine adrenaline and noradrenaline were 9, 5, 21, and 3 times upper reference value. MR: phaeochromocytoma (45 mm) in right adrenal. MIBG-scintigraphy: no extra-adrenal signal. In addition to this typical presentation she developed frequent fits with hunger, lethargy and visual disturbances, blood glucose 1.8–3.9 mmol/l, induced by sweet meals. A sweet meal challenge gave blood glucose 1.8 mmol/l, and simultaneously high C-peptide and insulin (1012 and 47 pmol/l). Pre-operative alphablockade with doxazosin normalised blood pressure and abolished headache, nausea and sweating, while her hypoglycemic fits persisted. β-blocker was intended because of moderate tachycardia and electrocardiographic abnormalities, and considered safe when alphablockade was effective. However, after the first tablet of pranolol 20 mg, she developed a severe attack with hypertension, pallor, headache, vomiting and Takotsubo-cardiomyopathy. The attack was curbed with intravenous nitroglycerin. After removal of her tumour she has been healthy, with normal blood glucose values and without hypoglycemic fits.
Discussion
Normally alphaadrenergic stimulation of β-cells inhibits, while βadrenergic stimulation increases insulin secretion. Three findings may indicate that her catecholamines have caused abnormal βadrenergic stimulation of insulin release: persistence of hypoglycemic fits after alphablockade; unusual response to the small βblocker dose, suggesting an abnormal βadrenergic tone; no fits postoperatively.
Conclusion
Our pheochromocytoma patient had the rare variant with hypoglycemic fits. They were hyperinsulinaemic, possibly caused by excessive βadrenergic stimulation of insulin secretion.

DOI: 10.1530/endoabs.37.EP1156

EP1157

An uncommon complication of post trans-sphenoidal surgery for pituitary adenoma

Hiang Leng Tan & Kurien John
Weston General Hospital, Weston-Super-Mare, UK.

Introduction
The commonest complications post trans-sphenoidal surgery is diabetes insipidus and the development of anterior pituitary hormone deficiencies. Other complications include meningitis, CSF leak, visual deterioration, haemorrhages and transient hyponatremia. We present a case of pituitary abscess 6 months post pituitary surgery who presented with viral meningitis and panhypopituitarism.
Case report
A 55-year-old lady presented with a 3 weeks history of tiredness, headache, visual disturbances and pyrexia. She had an uncomplicated trans-sphenoidal adenomectomy surgery (TSA) for TSH and GH secreting adenoma 6 months previously. She had evidence of pan hypopituitarism with a peak cortisol response of a short synacthen test of 280 nmol/l at 30 min, adrenocorticotropic hormone level of <5 ng/l, low gonadotrophin, low free T_3 and inappropriately normal thyroid-stimulating hormone. A lumbar puncture was done showing evidence of viral meningitis. Initial magnetic resonance imaging (MRI) of pituitary showed evidence of likely recurrence of her pituitary adenoma. However, due to the presence of pyrexia and viral meningitis a MRI pituitary with contrast was subsequently performed. This confirmed evidence of multiloculated pituitary abscess with optic chiasm compression. She was commenced on intravenous hydrocortisone, thyroxine, intravenous acyclovir and antibiotics and transferred to a neurosurgical centre for drainage of the abscess.
Conclusion
Pituitary abscess is a rare complication post transphenoidal surgery. Mortality is high and high index of suspicion is important as early surgical drainage is required for definitive treatment. In a patient with hypopituitarism and a sellar mass, pituitary abscess should be borne in mind if there are systemic signs of infection especially in a patient post pituitary surgery. When suspecting this condition, a MRI with contrast enhancement must be performed to look for evidence of ring enhancing lesion typical of abscess.

DOI: 10.1530/endoabs.37.EP1157

EP1158

Polyglandular autoimmune syndrome type 2 (Schmidt's syndrome)

Faiza Qari
King Abdulaziz, Jeddah, Saudi Arabia.

A 58-year-old Saudi female presented with fatigue, dizziness and generalised skin hyper-pigmentation. She was diagnosed as Hashimoto's hypothyroidism. She was diagnosed recently to be diabetic and her blood sugar was controlled with insulin. She reached menopause at the age of 36 years.

Lab results	Patient	Reference
FT_4	15;pmol/l	12–22
TSH	36 uIU/l	0.27–4.2
Antithyroglublin AB	1:1600	
Corisoal at 8.00	3.6 ug/dl	8–23
ACTH	850 pg/mL	20–80

BPis 90/60 mm/Hg sitting and 70/50 mm/Hg standing. Generalised hyperpigmentation of the skin. Diagnosis is polyglandular autoimmune syndrome type 2 (Schmidt's syndrome) was made on the basis of concomitant Hashimoto's hypothyroidism; premature ovarian failure; Addison's disease; IDDM.

DOI: 10.1530/endoabs.37.EP1158

EP1159

Sellar plasmacytoma masquerading as pituitary macroadenoma – a case report

Antonela Sabati Rajic[1], Matevž Škerget[2] & Sarah Gomezelj[3]
[1]Department of Endocrinology, University Medical Centre Ljubljana, Ljubljana, Slovenia, [2]Department of Hematology, University Medical Centre Ljubljana, Ljubljana, Slovenia, [3]Medical Faculty, University of Ljubljana, Ljubljana, Slovenia.

A 49-year-old male presenting with acute onset strabismus on left lateral gaze was admitted to the Endocrinology Department. The CT scan showed a 35×40×25 mm tumor mass, presumed to be a pituitary macroadenoma, in the sellar region which extended into the sphenoidal sinus, clivus, posterior ethmoidal cells, petrous part of the temporal bone and towards the nasopharynx. A MR scan of the head also revealed that the mass displaced the anterior pituitary gland and the infundibulum upwards. The MRI result was not typical for pituitary macroadenoma and raised the possibility of another tumour. A biopsy was performed and a specimen of the sphenoidal sinus mass was obtained. The histological examination revealed that the tumor was a moderately differentiated plasmacytoma with restriction to kappa light chains and a serum proteinogram showed a disturbance in the κ/λ ratio with a raise in the free κ light chains. A radiographic skeletal survey showed a suspect lesion of the 8th thoracic vertebra. Endocrinological assessment revealed indirect hyperprolactinaemia, secondary hypothyroidism and insufficiency of the pituitary-gonadal axis. After beginning the treatment with bortezomib and dexamethasone as well as radiotherapy, the patient's pituitary-adrenal axis also became insufficient. Plasmacytoma in the sellar region is very rare. There have been 33 cases reported in the literature insofar, but the number is even lower for cases where the sellar region was the first and/or only site of occurrence without prior diagnosis of multiple myeloma. The majority of sellar plasmacytomas described were diagnosed only after surgical treatment, whereas ours is the second case so far where the diagnosis was made prior to any surgical intervention in a patient without pre-existing multiple myeloma. It is also uncommon for plasmacytoma of the sellar region to present with a disturbance of the pituitary-peripheral axis, besides hyperprolactinaemia.

DOI: 10.1530/endoabs.37.EP1159

EP1160

Pituitary apoplexy case caused by Hanta virus ınfection

Semra Ayturk[1], Ahmet Bilal Genc[2], Selcuk Yaylacı[2], Oguz Karabay[3], Ali Tamer[2] & Mehmet Celik[1]
[1]Faculty of Medicine, Department of Endocrinology, Trakya University, Edirne, Turkey; [2]Department of Internal Medicine, Sakarya Education and Research Hospital, Sakarya, Turkey; [3]Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Sakarya University, Sakarya, Turkey.

Pituitary apoplexy (PA) is a rare but life-threatening medical emergency. Common predisposing factors include closed head trauma, blood pressure alterations, history of pituitary irradiation, cardiac surgery, anticoagulation, treatment with dopamine agonists, pituitary stimulation testing, and pregnancy. Hantaviruses belonging to the Bunyaviridae family are a group of rodent- or insectivore-borne single-strand ribonucleic acid (RNA) viruses. In humans, hantaviruses can cause haemorrhagic fever with renal syndrome or cardiopulmonary syndrome. About one third of the patients may occur bleeding in the brain, conjunctiva or gastrointestinal tract. Pituitary hemorrhage due to pituitary insufficiency have also been reported. We report the case of a patient, who the 62-years-old man was admitted to the emergency department with complaints of fever, severe headache and confusion. There was no disease in his history. He had not taken any medication or had bleeding disorder prior to this presentation. Leukopenia, thrombocytopenia, elevated liver enzymes and creatinine and panhypopituitarism was detected in laboratory investigations at intensive care. The patient underwent hemodialisis and stress-dose methylprednisolone was started. Because of fever, acut renal failure and thrombocytopenia etiology were thought to be viral infections. Serum sample of the patient was sent to National Reference Virology Laboratory for IFA and immunoblot test which revealed hantavirus IgM and IgG antibodies. Hantavirus seropositivity was determined by two tests. Magnetic resonance imaging revealed sella and suprasellar mass (22×23×30 mm) with evidence of acute hemorrhage and diagnosed as PA. The patient underwent transsphenoidal surgery. Histopathologic examination showed signs of recent bleeding. 12 months after surgery, the patient with persisten hypopituitarism is given steroid, L-thyroxine and testosterone treatment. Thus, physicians should suspect PA in a patient with hemorrhagic fever who develops a rapid onset of severe headache, even in a patient without a known pituitary adenoma.

DOI: 10.1530/endoabs.37.EP1160

EP1161

Pasireotide - the last treatment option in Cushing's disease - case report

Corina Galesanu[1,2], Adrian Condrea[2], Dan Niculescu[2], Alexandru Florescu[1], Catalin Buzduga[1,2], Liliana Moisii[1,2] & Vasile Ciubotaru[3]
[1]University of Medicine and Pharmacy 'Gr.T.Popa', Iasi, Romania; [2]University Hospital 'Sf.Spiridon', Iasi, Romania; [3]University Hospital 'Bagdasar-Arseni', Bucharest, Romania.

Introduction
The most common cause of Cushing's disease is ACTH secreting tumours of the pituitary gland. It is associated with high morbidity and mortality. Pasireotide, a potential therapy, has a unique, broad somatostatin-receptor–binding profile, with high binding affinity for somatostatin-receptor subtype 5.
Case report
We present the a 40-years-old man diagnosed in 2005 with Cushing's Disease for which a left adrenalectomy was performed (pathology report: diffuse and nodular adenomatous hyperplasia). In January 2006 given the persistence of hypercortisolism and the adenomatous hyperplasia in the right adrenal gland (49/29 mm), surgery was performed on this location also. After surgery, evolution was not good, the signs and symptoms of Cushing's Disease persisted, the urinary cortisol levels were very high and and for this Ketoconazole treatment (200 mg×3 per day) was initiated. Another surgery was performed on the left adrenal gland (CT showing a 1.5 cm nodule). Until 2008 the blood and urinary cortisol levels remain upper limit under Ketoconazole therapy. High ACTH and pituitary microadenoma require transsphenoidal surgery to practiced and which has proved to be ineffective. Another surgery is required which manages to normalize the ACTH and cortisol levels until 2012. Re-growth of ACTH requires begun the treatment with cyproheptadinum 4 mg (6/4 cp per day). When admitting of July 2014 ACTH and cortisol values are maintained above the limit: ACTH = 177 pg/ml, Cortisol = 15 μg/dl, UFC = 1753 nmol per day, and the MRI showing the pituitary microadenoma. We decide to start the treatment with Pasireotide (0.6 mg×2 per day) with a 2 months follow up (in October) when ACTH and cortisol have been normalized.
Conclusions
In our patient's case Pasireotide was the last and the only option, because the other proved inefficient in time. The significant decrease in cortisol levels in patients with Cushing's disease who received pasireotide supports its potential use as a targeted treatment for corticotropin-secreting pituitary adenomas.

DOI: 10.1530/endoabs.37.EP1161

EP1162

Lump it or leave it & bilateral adrenal macronodular hyperplasia: Case report and clinical insights

Namson S Lau & Nadia Manzoor
Liverpool Hospital, Sydney, New South Wales, Australia.

Clinical case
MG was a 57-year-old female when first referred to endocrinology for investigation of adrenal incidentaloma. Relevant medical history included poorly controlled hypertension on two agents, dyslipidaemia and history of minimal trauma fracture. Baseline labs (including 24 h urine collection) were unremarkable as was clinical examination (exception hypertension). Cortisol levels on two 1 mg Dexamethasone suppression tests failed to suppress. Dedicated CT adrenal study showed bilateral adrenal hyperplasia: left gland was largest. A diagnosis of bilateral adrenal macronodular hyperplasia with subclinical Cushings' syndrome was made. Further investigations showed high grade osteoporosis and normal results for aberrant receptors (TRH, GnRH, mixed meal and postural changes) and Short Synacthen test with 17-OH-P levels. Adrenal vein sampling was

performed that confirmed diagnosis. Immediate progress included continued hypertension now needing three agents; moderate weight gain and new minimal trauma vertebral fracture. Following discussion with MG regarding diagnosis and its associated complications (metabolic syndrome and osteoporosis), the treatment options of medical management of complications and monitoring vs medical treatment vs surgery, she elected for medical management and monitoring. Follow-up CT adrenal studies showed interval increasing size in both glands, persistent osteoporosis despite bisphosphonate treatment and moderate weight gain. Hypertension and dyslipidaemia were controlled. 4 years following initial diagnosis, MG elected for surgery and successfully underwent a laproscopic posterior extra-peritoneal left adrenalectomy. Post-operatively she does not require glucocorticoid therapy and reduced dosages of hypertensive medications. She continues to be followed up by endocrinology.

Discussion

This case highlights the challenges in recognising and managing bilateral adrenal macronodular hyperplasia and its complications. The natural history of the condition, role of investigations including for CAH and receptor testing, the value of adrenal venous sampling, imaging options and medical and surgical treatment options will all be explored.

DOI: 10.1530/endoabs.37.EP1162

EP1163

Clinical nonsecreting pituitary macroadenoma managed by cabergoline: anybody, anytime?

Amalia Ioana Arhire[1], Elena Iuliana Pascu[1], Simona Fica[1,2] & Carmen Gabiela Barbu[1,2]
[1]Elias University Hospital, Bucharest, Romania; [2]'Carol Davila' University of Medicine and Pharmacy, Bucharest, Romania.

Introduction

Therapeutic management of clinical nonsecreting pituitary adenomas with ophthalmological manifestations is certainly limited to surgery unless IHC from previous intervention could bring up new data.

Case report

A 16-year-old patient was admitted in February 2014 in our Endocrinology Department for short stature (−3.5 S.D.), in the context of an iatrogenic pituitary insufficiency. 7 months before, he had been diagnosed with pituitary macro-adenoma of 36/24/30 mm which invaded the sphenoidal sinus anteriorly and had a contact with the optic chiasm, causing left cecity. He undergone frontal adenomectomy, with a ACTH and TSH deficit that were currently substituted. Clinically: short stature (149.9 cm, −3.5 DS), underweight, BP=95/60 mm/Hg, Tanner stage P3G3, left temporal hemianopsia.Biologically: low IGF1 (−3 DS), maximum stimulated GH 0.226 during insulin induced hipoglicemia, normal testosterone, LH=1.9, normal ACTH, TSH and prolactin. The pituitary MRI showed an adenoma of 3.2/3.56/3.4 cm, the hand X-ray showed a bone age similar to the chronological age, with open growth cartilages and the visual field a left temporal hemianopsia. According to the family's choice not to reoperate, we decided to start the treatment with cabergoline as the adenoma had IHC prolactin, LH, FSH, TSH and GH staining. We started with a dose of 1 mg/week and progressively increased the dosage up to 3 mg/week, with visual field evaluation every 1–2 months and MRI after 6 months. The left hemianopsia improved and was stable for 3–5 months, the MRI showed no evolution, but after 6 months the patient developed right hemianopsia and nausea, so surgery was recommended.

Conclusion

Cabergoline treatment of nonsecreting tumors with IHC staining for D2 receptors is a new strategy with optimist results in recent studies; however, close monitoring is mandatory during the treatment in order to identify non-responders and assure an individualised therapeutic decision.

DOI: 10.1530/endoabs.37.EP1163

EP1164

Catecholamine-induced cardiomyopathy: pitfalls in diagnosis and management

Yaasir Mamoojee, Satish Artham, Wael Elsaify & Sath Nag
The James Cook University Hospital, Middlesbrough, UK.

Introduction

Cardiomyopathy as the initial presentation of phaeochromocytoma (PCA) is uncommon. Diagnostic workup and perioperative management may be challenging within this context. We report three cases of PCA presenting with cardiomyopathy to illustrate the pitfalls in diagnosis and management. None of the patients had typical adrenergic symptoms of catecholamine excess and all patients were well established on beta-blockers on presentation. All three patients had an adrenalectomy and a PCA was confirmed on histology.

Cases: Patient A: A normotensive 56-year-old male with dilated cardiomyopathy, was found to have an incidental longstanding right adrenal nodule. Plasma and urine metadrenaline levels were raised during decompensated heart failure and improved with treatment. However, a subsequent increase in metadrenaline levels was noted despite clinical and echocardiographic improvement of cardiac function. MIBG and Octreotide scans were both negative but CT of the right adrenal with wash out studies showed indeterminate characteristics. Patient B: A 66-year-old male was referred with a right adrenal mass. Previous investigations revealed severe left ventricular impairment and non-flow limiting coronary disease. Plasma and urine metadrenalines were raised and asymmetrical adrenal uptake was noted on an MIBG scan. Patient C: A 61-year-old female with type 1 Neurofibromatosis presented with Takotsubo cardiomyopathy. Fractionated metadrenaline levels were raised and a MIBG avid left adrenal lesion, corresponding to a left adrenal mass on CT scan, was found.

Conclusions

Interpretation of fractionated metadrenaline levels in the context of established cardiomyopathy is difficult as cardiac failure of any aetiology generates an adrenergic response. Screening all patients with idiopathic cardiomyopathy for catecholamine excess is highly likely to generate false positive results. However, a high index of suspicion should prompt further investigations of patients with idiopathic cardiomyopathy for occult an PCA. Peer reviewed guidelines are required to guide the investigation and management of suspected catecholamine-induced cardiomyopathy.

DOI: 10.1530/endoabs.37.EP1164

EP1165

Histiocytosis, a rare cause of hypopituitarism. Langerhans cell histiocytosis and Erdheim–Chester disease, two case reports of pituitary deficiency

Václav Hána, Mikuláš Kosák & Václav Hána
Third Medical Department, 1st Faculty of Medicine Charles University and General Faculty Hospital in Prague, Prague, Czech Republic.

Introduction

Langerhans cell histiocytosis (LCH) is a rare disease with incidence of 1–2 adults per milion/year. Pituitary function is affected in 30% of cases presenting almost always with diabetes insipidus. Other deficiencies such as GH, FSH+LH, TSH and ACTH follow. Erdheim–Chester disease is a rare Non-LCH described in several hundreds of cases in the world so far, with the pituitary function involvement in similar frequency as in LCH.

Case 1

A 36-year-old man has been treated for diabetes insipidus, central hypogonadism and severe GH deficiency of unknown origin since 2006. In 2014 MRI showed a hypothalamic lesion with involvement of pituitary stalk and other small lesions around IV. ventricle. PET/CT revealed maxillary and mandible lesions with adjacent soft and lymphatic tissue involvement. A biopsy from recently discovered scalp lesions, previously described as [foliculitis capitis] in the scalp, proved LCH. Otitis externa was another manifestation of LCH.

Case 2

A 42-year-old man has been diagnosed with isolated diabetes insipidus. MRI showed an infiltration of hypothalamus and pituitary stalk. Biopsy from suspicious papule on the arm did not reveal LCH as CD1a and S100 stains were negative. Additional PET/CT scan showed a multifocal bone involvement. The clavicle biopsy was in agreement with the skin papule biopsy and diagnosed an Erdheim–Chester disease.

Conclusions

Histiocytosis should be considered in case of a diabetes insipidus with/without other pituitary deficiency and hypothalamic lesion. Other organs such as bones, skin, lungs, lymphatic tissue and others can also be involved and PET-CT scan can reveal it. A biopsy from the extrapituitary lesion can lead to the diagnosis.

DOI: 10.1530/endoabs.37.EP1165

EP1166

A rare case of primary empty sella syndrome and growth hormone excess in a patient with neurofibromatosis type 1

Pascu Elena Iuliana[1], Epure Mihaela[1], Arhire Amalia Ioana[1], Martin Sorina[1,2] & Fica Simona[1,2]
[1]Endocrinology Department, Elias Emergency Hospital, Bucharest, Romania, [2]Endocrinology Department, Carol Davila University of Medicine and Pharmacology, Bucharest, Romania.

Introduction
Neurofibromatosis type 1 (NF1) is the most common type of NF, and accounts for about 90% of all cases. Primary empty sella syndrome (ESS) results from herniation of arachnoid mater into the pituitary fossa. Since it has been demonstrated that the small anterior pituitary size reflects loss of neurofibromin expression in the hypothalamus, leading to reduced GHRH, pituitary GH and IGF1 production, we agree that IGF1 and GH increased in our patient can be challenging.
Case report
We report the case of a 33-year-old woman, diagnosed in childhood with NF1, with a single spontaneous menstrual cycle at 14 years, secondary amenorrhea and oestroprogestative substitution treatment ever since, diagnosed with primary ESS, hydrocephaly and central ventricular system malformation at 18 years. Physical examination revealed six café au lait macules on the trunk and neck, multiple cervical, supraclavicular and upper thorax plexiform neurofibromas. Blood pressure was 115/100 mm/Hg, without orthostatic hypotension. The fluid intake was normal. She had no hystory of head trauma, pregnancy or childbirth. Lab tests:IGF1 = 413 ng/ml (115–307 ng/ml) ACTH = 12.6 pg/ml, TSH = 0.893 μIU/ml, FT4 = 0.851 ng/dl, TPOAb < 10 UI/ml ($n < 35$), PTH = 46.5 pg/ml, 0800 h serum cortisol = 12.9 μg/dl, plasmatic metanephrines = 15.1 pg/ml ($n < 90$), plasmatic normetanephrines = 35.8 pg/ml ($n < 180$). Oral glucose tolerance test showed unsuppressed GH on glucose load (nadir GH = 1.710 ng/ml). Thyroid, breast, abdominal and pelvic ultrasound were normal. Bone densitometry: z-score spine = −2.5 s.d. Pituitary MRI:empty sella without pituitary microadenoma. We consider that this is either infarction of a pituitary microadenoma or ectopic secretion of GHRH requiring further evaluation.
Conclusion
ESS is a rather frequent neuroradiological finding in the general population and can be associated with hypopituitarism. GH deficiency is more common in patients with NF. Since this rare case presents a young patient with NF, ESS and an uncommon excess of GH, careful evaluation, diagnosis and follow-up appears to be essential.

DOI: 10.1530/endoabs.37.EP1166

EP1167

Gonadotrophin secreting pituitary adenoma with hypersecretion of testosterone and testicular enlargement

Murali Ganguri[1], Naveen Aggarwal[1], Alistair Jenkins[2], Abhijit Joshi[3], Colin Saysell[3] & R A James[1]
[1]Department of Endocrinology, Royal Victoria Infirmary, Newcastle upon Tyne, UK; [2]Department of Neurosurgery, Royal Victoria Infirmary, Newcastle upon Tyne, UK; [3]Department of Pathology, Royal Victoria Infirmary, Newcastle upon Tyne, UK.

Gonadotroph pituitary adenomas are common but majority of them are classified as non-functional as they do not lead to features of hormonal excess. Functional gonadotroph adenomas are rare and there are only few small series or individual case reports about these.
Case report: 45-year-old gentleman presented with headaches, progressive visual failure and complaint of excessive tiredness. He had normal libido and had an 8-year-old child. On examination, he had bitemporal hemianopia and bilaterally enlarged testes (>40 ml bilaterally). His MRI showed a large pituitary macroadenoma (35 × 29 × 26 mm) with suprasellar extension and displacing the optic chiasma. His blood results showed high normal haemoglobin of 180 g/l (130–180) with borderline high haematocrit of 0.51 l/l (0.40–0.50). Sex hormone profile was as follows: LH: 10.5 IU/l (3.0–13); FSH: 15.7 IU/l (1.3–9.2); Testosterone: 43.4 nmol/l (9–25); free Testosterone 1257 pmol/l (215–760); Sex Hormone Binding Globulin 26 nmol/l (15–48). Alpha sub-unit was also elevated at 2.55 IU/l (NR < 1.0). His thyroid functions were as follows: TSH: 7.61 mU/l (0.3–4.7), FT_4: 6.0 pmol/l (9.5–21.5); FT_3: 2.7 pmol/l (3.5–6.5). Prolactin was mildly high at 982 mIU/l (0–450). GH and IGF1 were normal at 0.13 μg/l and 14 nmol/l (7–28) respectively. His baseline cortisol was low at 75 nmol/l. He was started on Dexamethasone and Levothyroxine and underwent trans-sphenoidal pituitary adenomectomy. He made an uneventful recovery apart from transient diabetes insipidus. The histology was consistent with pituitary adenoma with scattered FSH positive cells and very rare LH positive cell. In the post-operative period, his LH, FSH & Testosterone levels were 0.7 IU/l, 3.0 IU/l and <1.0 nmol/l respectively. His visual fields also improved significantly. He is continuing on steroids and levothyroxine. The patients reported earlier had either high testosterone levels or testicular enlargement. The authors could not find any case report of a patient with both, high testosterone level and testicular enlargement, secondary to functional gonadotrophinoma.

DOI: 10.1530/endoabs.37.EP1167

EP1168

Adrenal cevernous hemangioma

Miomira Ivovic[1,2], Vladan Zivaljevic[1,2], LJiljana Marina[1], Svetlana Vujovic[1,2], Milina Tancic-Gajic[1,2], Zorana Arizanovic[1], Dragana Rakovic[1] & Dragan Micic[1,2]
[1]Clinic for Endocrinology, Diabetes and Metabolic Disease, Clinical Center Serbia, Belgrade, Serbia; [2]Belgrade University School of Medicine, Belgrade, Serbia.

Adrenal hemangioma is a rare adrenal tumour usually presented as incidental finding in asymptomatic patients. Due to its radiographic features sometimes it's difficult to differentiate them from other malignant lesions. We present a 55-years-old men admitted to our department with adrenal incidentaloma size 5 × 4 cm confirmed by MSCT scan. Active phaeochromocythoma was excluded by normal urinary catecholamines. Endocrine evaluations revealed normal midnight cortisol, with post 1mg-DST cortisol suppression and normal basal ACTH. PRA and Aldosteron were in normal range with normal ALD/PRA ratio. According to MSCT tumour had some malignant neoplastic features. Surgery was performed. Intraoperative findings showed adrenal tumour about 5 cm sizes without signs of local infiltration or lymphadenopathy. Tumour was completely removed with adrenalectomy. Pathophysiology showed cavernous and partially capillary hemangioma with hyperplasia of the rest of adrenal gland. 6 months later patient was retested and results show normal function of the left adrenal gland. Most of adrenal cavernous hemangioma was non-functional and surgical removal was the right choice of therapy. They should be also the part of differential diagnosis of adrenal incidentaloma.

DOI: 10.1530/endoabs.37.EP1168

EP1169

Oncocytic adrenal cortical adenoma presenting as Cushing's syndrome: an exceptional clinical entity

Maria Molina Vega, Araceli Muñoz Garach, Silvia Maraver Selfa, Ana Gomez Perez, Isabel Cornejo Pareja, Cristina Diaz Perdigones, Isabel Mancha Doblas & Francisco Tinahones Madueño
Hospital Clinico Universitario Virgen de la Victoria, Malaga, Spain.

Introduction
Oncocytomas are tumours composed by oncocytes, cells with granular and eosinophilic cytoplasm filled with mitochondria. It is a neoplasm that can arise in several organs (more commonly described in the kidney, salivary gland and thyroid). Oncocytoma arising in the adrenal gland is a rare finding. Most of them are benign and non-functioning and are detected incidentally. However, functional adrenal oncocytomas presenting as Cushing's syndrome and phaeochromocytoma have been reported.
Case report
55 years old woman with progressive weight gain in the last year. Medical history: smoker, arterial hypertension, dyslipidemia, gastroesophageal reflux disease and past infection with the hepatitis B virus. She had developed edema of her face, abdomen and ankles and had frequent headaches. Physical examination: truncal and centripetal obesity, thin extremities with muscle atrophy, plethoric moon face, echymoses and hirsutism. Blood pressure: 120/85 treated with losartan 50 mg/24 h, amiloride hydrochlorothiazide 5/50 mg/24 h and atenolol 50 mg/24 h. Laboratory evaluation: fasting blood glucose 86 mg/dl, total cholesterol 218 mg/dl, HbA_{1c} 6.3%, TSH 0.96 μIU/ml, serum cortisol (0800 h) 22 μg/dl (5–25), serum cortisol (after 1 mg overnight dexamethasone suppression) 10 μg/dl, serum cortisol (after 0.5 mg dexamethasone every 6 h for 48 h suppression) 27 μg/dl, urinary free cortisol repeatedly reased (593, 388 μg/24 h), ACTH 1 pg/dl, rest adrenal hormonal profile normal. Computed tomography: 2.2 cm mass in the right adrenal gland. From these findings, the final diagnosis for this patient was Cushing's syndrome and we decided laparoscopic right adrenalectomy. Histopathology: adrenal adenoma with encapsulated oncocytoma without capsular invasion. The patient is receiving glucocorticoid replacement

therapy 6 months after the surgery with progressive reduction. She is waiting to see clinical and analytical evolution to suspend such treatment.
Conclusion
Adrenocortical oncocytoma, although extremely rare, should be considered in the differential diagnosis in adrenal masses. They are usually non-functional and benign but few cases are functioning tumours and may cause Cushing's syndrome. To make a correct diagnosis, biochemical, clinical and histological features must be analysed together.

DOI: 10.1530/endoabs.37.EP1169

EP1170

Adrenal insufficiency revealing pseudotumorale surrénale tuberculosis

Samir Ait Abderahmane, Meriem Bensalah, Yamina Aribi, Lila Brakni, Samia Ouldkablia & Zahra Kemali
Central Hospital of Army, Algiers, Algeria.

Adrenal tuberculosis was first described by Thomas Addison in 1855, Isolated adrenal tuberculosis is rare and between represents 1–2% of the aetiologies of adrenal masses called expired incidentalomas. We report the case of a related Addison's disease is a progressive adrenal tuberculosis which could benefit from exploration and a tomography monitoring on anti tuberculosis treatment. Patient aged 35 years presented himself to medical emergency with clinical surgical nickname, the diagnosis of adrenal insufficiency decompensation was made. Our patient underwent adequate replacement therapy, with correction of electrolyte disturbances. The aetiological investigation concluded in adrenal tuberculosis on the basis of arguments. History of pulmonary tuberculosis treated, melanodermia gradual onset, progressive weight encrypted fall has 16 kg in 3 years, TA figures tend to decline, Malaise hypoglycemic with difficulty fasting month of Ramadan. TST positive tuberculin 25 mm.La chest X-ray shows pulmonary tuberculosis effects and abdominal CT shows bilateral adrenal hypertrophy presence of multiple nodules that larger situated right 21 mm major axis. After a treatment based TB established for 6 months, a radiological objective control complete disappearance of radiological lesions surrenalien. Un base cortisol is collapsed income 89 ng/l. In light of this observation we update on this rare disease. Adrenal tuberculosis can be discovered on the occasion of the setting evidence of adrenal mass was the initial phase of bacillary disease, there adrenal hypertrophy before the appearance hormonal insufficiency.

DOI: 10.1530/endoabs.37.EP1170

EP1171

Three cases of successful pregnancy outcomes after different methods of therapy in women of acromegaly apart from remission of the disease

Natalia Molitvoslovova[1], Andrey Grigoriev[1], Yuri Trunin[2] & Olga Oleynik[1]
[1]Endocrinology Research Center, Moscow, Russia; [2]Burdenko Neurosurgery Institute, Moscow, Russia.

Reports of pregnancy in acromegalic women are uncommon.
Case 1: Patient K., 25-year-old., 01/04/2008 – transsphenoidal adenomectomy in connection with active acromegaly (GH/OGTT – 47.2–64.0–38.0–29.6–28.7 ng/ml; macroadenoma 19×14×12 mm with compression of optic chiasm). Postoperative remission of the disease, recovery of menstrual function without additional therapy. At the end of August 2008 the patient became pregnant, in the beginning of June 2009 – childbirth. After 6 months – the second successful pregnancy. The both children are wellbeing till now.
Case 2: Patient Yas.,32-year-old., 24/02/2005 – partial transsphenoidal adenomectomy without remission due to spreading macroadenoma into left cavernous sinus around ICA. After surgery patient received additional therapy with SSA (Somatulin 30 mg twice a week till 2006, then Sandostatin LAR 40 mg in combination with cabergoline 1 mg a week) without cure of the disease: IGF1 is not low then 770 ng/ml (62–280). 03/04/08 – radiotherapy ('Novalis'), 22 G. After 1 year – spontaneous pregnancy. Due to severe headache in view of active disease patient independently continued therapy with Sandostatin LAR 40 mg during all period of pregnancy. In the beginning of March 2010 – childbirth. The boy is wellbeing till now.
Case 3: Patient P., 30-year-old. Primary infertility during 10 years. Two-fold partial transsphenoidal adenomectomy (in 1998 and 2001) without remission due to macroadenoma with supra-infra-latero-cellar extension. In 2002 – conventional gamma-therapy, 50 G. In one year after radiotherapy – active acromegaly (GH-25 ng/ml, IGF1 – 690 ng/ml) and spontaneous pregnancy with successful outcome. The boy is wellbeing till now. After childbirth SSA therapy have been initiated.

DOI: 10.1530/endoabs.37.EP1171

EP1172

An unusual cause of central diabetes insipidus

Paraskevi Kazakou, Frederic Vandergheynst, Bruno Couturier, Nicolas Dumarey, Daniel Van Gansbeke, Agnieszka Pozdzik, Sandrine Rorive & Agnes Burniat
Erasme Hospital, Brussels, Belgium.

Introduction
In 30–50% of cases central diabetes insipidus (CDI) is idiopathic. Other causes include tumours, pituitary surgery, cranial trauma or infiltrative diseases. Long-term medical follow-up is crucial given that idiopathic CDI can be the earliest sign of an evolving process (inflammatory or tumoural).
Case report
We report the case of a 23-year-old woman who presented with isolated polydipsia and polyuria. The diagnosis of isolated CDI was established. Magnetic resonance imaging of the pituitary gland showed thickening of the pituitary stalk and loss of normal hyperintense signal of the posterior pituitary on T1-weighted images. A ^{18}F-FDG PET/CT revealed a tumour-like lesion in the right kidney which was confirmed by a renal contrast-enhanced ultrasonography (CEUS). Granulomatous with polyangiitis (GPA) was suspected on the basis of associated maxillary sinus hypermetabolism on PET/CT and plasmatic anti-MPO ANCA positivity. Strikingly, urinalysis and renal function were normal. Furthermore sinus biopsy revealed no granulomatous inflammation. Ultrasound control performed six months later showed that the right renal mass had doubled in diameter and demonstrated new lesions in the left kidney. Renal function and urinary sediment still remained normal. Finally, US-guided biopsy of the right renal tumour revealed granulomatous inflammation consistent with the diagnosis of GPA.
Conclusions
GPA is an ANCA-associated systemic vasculitis which classically affects the upper and lower respiratory tracts and kidneys. Pituitary involvement is very rare. Renal impairment is usually characterised by glomerulonephritis with hematuria and/or proteinuria leading to progressive renal failure. Only 16 cases of GPA with renal pseudotumours have been reported. To our knowledge this is the first case combining CDI and subsequent bilateral renal tumours in the setting of GPA. This affection should be considered in the differential diagnosis of CDI. Early diagnosis and initiation of treatment could minimize the risk of irreversible pituitary function loss.

DOI: 10.1530/endoabs.37.EP1172

EP1173

Longest survival with central diabetes insipidus; more than 30 years without and 25 years with desmopressin treatment

Didem Ozdemir[1], Sefika Burcak Polat[1], Yunus Halil Polat[1], Reyhan Ersoy[2] & Bekir Cakir[2]
[1]Department of Endocrinology and Metabolism, School of Medicine, Yildirim Beyazit University, Ataturk Education and Research Hospital, Ankara, Turkey; [2]Department of Internal Medicine, School of Medicine, Yildirim Beyazit University, Ataturk Education and Research Hospital, Ankara, Turkey.

Introduction
Diabetes insipidus (DI) is a disease characterized by excessive thirst, polydipsia and excess diluted urine caused by insufficiency of antidiuretic hormone or renal resistance to its effect. Although it is generally a benign condition, severe hypernatremia and hypertonicity may cause death if water loss is not compensated.
Case report
A 72-years-old man admitted to our clinic for routine control. In medical history, he told that when he was about 9 years, polyuria and polydipsia had started and he was diagnosed to have DI when he was 17 years old in 1959. At that time, he was told to drink water as much as possible since there was not any drug available in our country. He had been drinking about 15–16 l of water in those years. About 25 years ago, desmopressin became available in our country and the patient had started desmopressin treatment. From then on, polyuria and polydipsia had

resolved and the dosage was progressively increased to 3×20 mcg/day. He did not have any other chronic disease except hypertension regulated with amlodipin. In laboratory examination, serum sodium was 141 mmol/l, potassium 4.1 mmol/l, urinary density 1014, serum osmolality 291 mlOsm/l and urinary osmolality 486 mlOsm/kgwater. His anterior hypophysial hormones were normal and magnetic resonance imaging revealed a normal hypophysial gland with a height of 4.3 mm.

Conclusion

To our knowledge, the longest follow-up time reported in studies or case reports including patients with central DI in the literature does not extend beyond 30 years. Our patient has the longest survival of more than 55 years of which 30 years passed without any medical treatment. This is supportive for the fact that loss of urine can be compensated and water balance can be maintained as long as thirst mechanisms work and water intake is provided.

DOI: 10.1530/endoabs.37.EP1173

EP1174

Positive MIBG scan in a patient with adrenal failure secondary to lymphoma: a coexistent paraganglioma or false positive involvement?

Didem Ozdemir[1], Sefika Burcak Polat[1], Betul Asan[2], Aydan Kilicarslan[3], Sabire Y Aksoy[4], Seyda Turkolmez[4], Reyhan Ersoy[1] & Bekir Cakir[1]
[1]Department of Endocrinology and Metabolism, School of Medicine, Yildirim Beyazit University, Ataturk Education and Research Hospital, Ankara, Turkey; [2]Department of Internal Medicine, School of Medicine, Yildirim Beyazit University, Ataturk Education and Research Hospital, Ankara, Turkey; [3]Department of Pathology, School of Medicine, Yildirim Beyazit University, Ataturk Education and Research Hospital, Ankara, Turkey; [4]Department of Nuclear Medicine, School of Medicine, Yildirim Beyazit University, Ataturk Education and Research Hospital, Ankara, Turkey.

Introduction

We report stage IV B cell lymphoma in a patient presenting with adrenal failure and an intraabdominal mass which imaging techniques were suggestive for paraganglioma.

Case report

A 71-years-old woman admitted to our emergency clinic with severe fatigue and stupor. She was diagnosed to have primary adrenal failure since serum ACTH was 229 pg/ml and cortisol response to 250 µg co-syntropin was 6.17 µg/dl. In abdominal MRI, bilateral adrenal enlargement and a 35×31 mm paraaortic lesion consistent with paraganglioma (heterogenous, markedly increased contrast uptake, milimetric cystic foci) were detected. ^{123}I-MIBG showed diffuse uptake in the lesion. 24 h urine metanephrin, normetanephrin and VMA levels were moderately increased. She did not have persistent or intermittent hypertension. During investigation for the cause of adrenal failure, multiple mediastinal and hilar lymph nodes (24×7 mm the biggest) were observed in thoracal CT and a lesion of 94 mm destructing cortex of left iliac crest and extending to soft tissue was detected in pelvic MRI. 18F-FDG PET/CT confirmed high uptakes with high SUVmax indexes in the lesion inferior to the left adrenal gland, bilateral adrenal glands, paravertebral and mesenteric lymph nodes, intestinal serosal surfaces and left iliac crest. A CT-guided biopsy was taken from the lesion surrounding iliac crest and the histopathological result was high grade B cell lymphoma infiltration. Rituximab-CHOP chemotherapy treatment was started.

Conclusion

To our knowledge, coexistent paraganglioma and lymphoma was not reported in the literature previously. However, since we did not have histopathological confirmation, false positive MIBG uptake secondary to lymphoma could not be excluded. Although ^{123}I-MIBG is known to have a sensitivity of 77–90% and specificity of 88–99% for localizing paragangliomas, lymphoma might be one of the causes of false positivity in addition to some other rare causes such as angiomyolipoma.

DOI: 10.1530/endoabs.37.EP1174

EP1175

Synacthen induced phaeochromocytoma crisis, an unusual presentation

Ali Aldibbiat[1], Murali Ganguri[1], RD Bliss[2] & Andy James[2]
[1]Department of Endocrinology, Royal Victoria Infirmary, Newcastle Upon Tyne, Tyne and Wear, UK; [2]Department of Endocrine Surgery, Royal Victoria Infirmary, Newcaslte upon Tyne, UK.

75 male was referred to endocrine service with incidental pituitary macroadenoma measuring 4.2×3.1×3.3 cm noted on MRI-C-Spine done for ankylosing spondylitis with Atlanto-axial joint instability. He had reduced secondary sexual characteristics and left quadrantanopia. Endocrine studies confirmed thyrotroph and gonadotroph failure but normal lactotroph and HPA axis. He underwent trans-sphenoidal tumour resection followed by external beam radiation due to tumour residuum. His quadrantanopia resolved completely and he was started on annual pituitary assessment. 2 years later he developed palpitations and collapsed following Synacthen injection for short Synacthen test (SST). He made full recovery and initial work up demonstrated no clear cause. A repeat SST 6 month later resulted in palpitations and near collapse. An evolving history of frequent episodes of palpitations and sweating accompanied by headache over the previous months was noted, which raised suspicion of pheochromocytoma. Plasma metanephrines then were marginally elevated (metadrenaline 1140 (80–510) pmol/l, normetadrenaline 3833 (120–1180) pmol/l). This rose further in the following 3 months (metadrenaline 3008 pmol/l, normetadrenaline 5387 pmol/l) and 24 urine analsysis demonstrated raised indices to creatinine (metadrenalines/creatinine 1.14 (0–0.3) umol/mmol, normetadrenaline/creatinin 0.76 (0–0.35) umol/mmol). CT-abdomen demonstrated a suspicious L-adrenal mass measuring 4.5×4.3 cm. MIBG scan showed uptake in the region of L-adrenal consistent with a neuroendocrine tumour. Alpha-blockade was established and patient later underwent L-adrenalectomy. Histopathology confirmed pheochromocytoma. Metanephrines normalised post-operatively but SST demonstrated inadequate adrenal response. He is currently on glucocorticoid replacement and annual pituitary assessment. This case demonstrates synacthen-induced pheochromocytoma crisis. There are several case reports of exogenous glucocorticoid-induced pheochromocytoma crises but no reports of Synacthen/ACTH-induced crisis were found. The likely mechanism is the effect of glucocorticoid surge secondary to synacthen stimulation leading to augmented effect on enzymes involved in catecholamine biosynthesis and release, e.g. phenylethanolamine N-methyltransferase (PNMT).

DOI: 10.1530/endoabs.37.EP1175

EP1176

Ectopic ACTH-secreting pituitary adenomas located in the sphenoid sinus: an overview

Philip C Johnston[1], Laurence Kennedy[1], Robert J Weil[2] & Amir Hamrahian[1]
[1]Department of Endocrinology, Diabetes and Metabolism, Cleveland Clinic, Cleveland, OH, USA; [2]Department of Neurosurgery, Cleveland Clinic, Cleveland, OH, USA.

Background

Ectopic pituitary adenomas are defined by the presence of adenomatous pituitary tissue outside the sella and distinctly separate from the pituitary gland. Ectopic ACTH-secreting pituitary adenomas (EAPAs) are a rare cause of Cushing's syndrome. Detecting these radiologically can prove difficult, in part, due to their typically small size and unpredictable anatomical location.

Aim

We reviewed the current literature on all previously reported EAPAs within the sphenoid sinus.

Results

Twenty cases of EAPAs have been reported in the literature to date. In most cases, ectopic ACTH pituitary adenomas within the sphenoid sinus will manifest with symptoms of hormonal excess, have an obvious sphenoid sinus mass on pre-operative imaging and will demonstrate resolution of hypercortisolism after surgical excision if located and removed.

Conclusions

In ACTH-dependent Cushing's syndrome, if, despite comprehensive testing, the source of excess ACTH remains occult (including negative work up for ectopic ACTH syndrome) thought should be given to the possibility of the patient harbouring an EAPA. Careful review of the neuroimaging to identify potential lesions, especially when pituitary imaging is not conclusive, is imperative. In the context of negative 'MR' imaging, the presence of EAPAs should be considered. Appropriate investigation and resection of such lesions may prevent unwarranted hypophysectomy, radiotherapy and/or adrenalectomy and result in long term and persistent remission.

DOI: 10.1530/endoabs.37.EP1176

EP1177

Cushing's disease and co-existing phaeochromocytoma

Philip C Johnston[1], Pablo Recinos[2], Laurence Kennedy[1] & Amir Hamrahian[1]
[1]Department of Endocrinology, Diabetes and Metabolism, Cleveland Clinic, Cleveland, OH, USA; [2]Department of Neurosurgery, Cleveland Clinic, Cleveland, OH, USA.

Clinical presentation
We report a 46 year old female who presented with a 1 year history of bruising, thin skin and weight gain. In addition; she reported flushing of her chest, heat intolerance, palpitations and abdominal pain. On clinical examination she appeared cushingoid, blood pressure was elevated at 160/98 mm/Hg.
Investigations
Biochemical investigations indicated ACTH-dependent Cushing syndrome: 24 h UFC 300 μg (0–50), ACTH 119 pg/ml (8–42); midnight salivary cortisol 950 ng/dl (<100). MRI pituitary demonstrated a sellar lesion; 14×9×9 mm suggestive of a pituitary macroadenoma. To investigate the symptoms of flushing and palpitations, plasma fractionated catecholamines and metanephrines were performed and were elevated; norepinephrine 822 pg/ml (80–520), epinephrine <10 pg/ml (10–200), dopamine <20 pg/ml (0–20), normetanephrine 1250 pg/ml (18–101), metanephrine 34 pg/ml (12–67). CT abdomen revealed a lipid poor right adrenal mass measuring 17×36 mm with Hounsfield units of 47, consistent with a phaeochromocytoma.
Management
The patient started phenoxybenzamine and subsequently uptitrated the dose for three weeks prior to elective adrenalectomy. A robotic right trans-abdominal lateral adrenalectomy was performed without complications, histology confirmed phaeochromocytoma. One month post-adrenalectomy plasma fractionated catecholamines and metanephrines were normal. The patient continued to be hypercortisolemic post-op. 6 weeks after adrenal surgery transsphenoidal resection of the pituitary mass was performed, the histology revealed an adenoma which was diffusely positive for ACTH, it did not stain with any other anterior pituitary hormones. At 3 months post-pituitary surgery, she had normal plasma metanephrines and 24 h UFC levels with no visible residual disease on pituitary MRI.
Discussion
Phaeochromocytoma is associated with excess morbidity and mortality if undiagnosed, it was therefore fortuitous that this diagnosis was made prior to pituitary surgery. Clinicians should be alert to the about rare association of phaeochromocytoma in patients with clinically significant pituitary adenomas, and pursue further work up if clinically indicated.

DOI: 10.1530/endoabs.37.EP1177

EP1178

Cushing's disease from an ectopic parasellar adenoma

Philip C Johnston[1], Laurence Kennedy[1], Amir H Hamrahian[1] & Robert J Weil[2]
[1]Department of Endocrinology, Diabetes and Metabolism, Cleveland Clinic, Cleveland OH, USA, [2]Department of Neurosurgery, Cleveland Clinic, Cleveland, OH, USA.

Background
Most cases of Cushing's disease originate from the pituitary, rarely the source of excess ACTH is from an ectopic pituitary adenoma.
Case
A 34-year-old woman had a 12-month history of a labile mood, weight gain, easy bruising, irregular menses and hypertension, she appeared cushingoid. Biochemical investigations demonstrated hypercortisolism: 24 h urine-free cortisol 520.7 μg (4–50), ACTH 152 pg/ml (8–42); midnight salivary cortisol 510 ng/dl (<100), 0800 h serum cortisol 28.5 mcg/dl (6.5–26) after a 1 mg overnight dexamethasone suppression test (DST). There was a 70% suppression of cortisol after an overnight high dose (8 mg) DST, and a 50% increase in ACTH during a corticotropin releasing hormone (CRH) test. MRI of the sella revealed an atypical enhancing mass (0.7×0.9×0.5 cm) lying above the pituitary gland, the pituitary gland was normal. Transsphenoidal exploration without inferior petrosal sinus sampling (IPSS) was undertaken. A lesion located wholly in the suprasellar intracranial space, with its inferior aspect lying on but not transecting the diaphragm sella, was removed. No tumour was identified within the sella or pituitary. Pathology revealed a pituitary adenoma, with ACTH immunopositivity. At 6 months follow-up she remains in remission, with preservation of anterior pituitary function.
Discussion
Various locations of ectopic pituitary adenomas have been reported, including the sphenoid sinus, nasopharynx, intracavernous sinus. Ectopic pituitary tumours have been proposed to arise mainly from pituitary rest cells from the embryonic remnants of Rathke's pouch, from aberrant migration of pituitary cells or from neoplastic transformation of the pharyngeal pituitary. They can be difficult to diagnose because of their small size and unusual locations.
Conclusion
In patients with Cushing's disease, careful preoperative review of sellar imaging is imperative. These ectopic tumours are not always visible on imaging, and may explain why some patients with Cushing's disease have residual hypercortisolism after hypophysectomy.

DOI: 10.1530/endoabs.37.EP1178

EP1179

Two cases of observation of teenagers after prostatectomy volume transnasal pituitary education followed by recombinant growth hormone therapy Dzhintropinom (Eurofarm)

Mukhlisa Shakirova[1,2], Yulduz Urmanova[1,2] & Shakhlo Babakhodgaeva[1,2]
[1]Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan; [2]The Center of Endocrinology, Tashkent, Uzbekistan.

Purpose
To examine two cases of teenagers after transnasal removal of pituitary volume of education followed by recombinant growth hormone therapy Dzhintropinom (Eurofarm).
Materials and methods
During the period of 2014 in the department of paediatric endocrinology and neuroendocrinology RSNPM Endocrinology Center MoH (Tashkent), we examined two male patients, including the patient F., 2.5 g of a craniopharyngioma, and the second patient For 15 years with inactive pituitary adenoma. Patients underwent the following range of studies, including clinical, biochemical blood tests and urine tests, radioimmunoassays hormonal methods of blood tests (prolactin, IGF1, GH, TSH, ACTH, LH, FSH, free testosterone, cortisol, thyroxine), ECG, ultrasound genitals and others. All patients underwent MRI of the pituitary gland. Both patients in 2013 was carried out surgery – transnasal pituitary prostatectomy. In both postoperative patients developed panhypopituitarism: diabetes insipidus, GH deficiency (0.03 nmol/ml at a rate of greater than 2 nmol/l), IGF1 (<35 ng/ml), and hypogonadotropic hypogonadism and short stature patient K. 15 l. In this regard, both patients were assigned to hormone replacement therapy, which included desmopressin, levothyroxine, and genetically engineered growth hormone Dzhintropin (Eurofarm). The latter was assigned based 0.033 ug/kg per day, daily, subcutaneously, in the evening, in the forearm, within 6–8 months.
Results
Based on the investigations, it was found that both patients showed a positive trend during therapy Dzhintropinom, namely significantly increased basal and stimulated (with sample klofellinom) levels of growth hormone. Furthermore, there was a noticeable improvement in the dynamics of growth of the body, namely an average of 6 months to 6 cm.
Conclusions:
patients (children and adults).

DOI: 10.1530/endoabs.37.EP1179

EP1180

The case of a combination of pituitary hypoplasia and achondroplasia have a child (boy 6 years old)

Feruza Khodgaeva, Yulduz Urmanova, Shakhlo Babakhodgaeva & Nazira Rikhsieva
Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan.

Purpose
To describe the case of a combination of pituitary hypoplasia and achondroplasia have a child (boy).
Material and methods
Under our outpatient observation is a boy Abdulahatov S., born in 2008, lives in Samarkand. From history: The child was born in the closely related parents' marriage (sisters' children). Height at birth 50 cm, weight 3000 g, cried and took the breast immediately. Psycho-motor development – late. Constantly under the supervision of a paediatrician, getting a massage. Addressed to the endocrinologist for the first time in 2014. In RSSPMC Endocrinology MoH patients underwent the following range of studies, including clinical, biochemical studies - complete blood count, radioimmunoassay methods hormonal blood tests (prolactin, IGF1, GH, TSH, cortisol, thyroxine), ECG, ultrasound of internal organs, pituitary MRI, X-ray of hand and spine.
Results and discussion
According to parents, the patient complains of stunting, trouble walking. On examination it was found: objective: Growth 103, 5 cm, weight – 29 kg. Growth Deficit – 20 cm, underweight – 9 kg. Pubertal status: Ah0Rh0, testis 3.0×3.0 ml, penis length of 1.0 cm. On the side of hormonal studies: STG – 1.4 mIU/l (normal in children aged 5–16 years 2.1±0.53 mIU/l, St. T_4 – 124 nmol/L (60–160), TSH – 1.9 mIU/l (normal 0.17±4.05), IGF1 – 101 nmol/l. MRI sella (from 01.12.2014 g) was discovered pituitary hypoplasia: height 0.1 cm anteroposterior size – <0.4, width – up to 0.4 cm. On radiographs of the hand (from 02.12.2014 was): bone age from 3 to 24 months, the appearance of a violation of the sequence of points of ossification. Growth areas are open, narrowed, shortening of the phalanges. Cystic fibrosis? Gipohondroplaziya? On radiographs of the spine (from 02.12.2014 city). S-shaped scoliosis of the spine. Dysplasia of both hips, thighs complicated dislocation on both sides. Thus, on the basis of the foregoing, the clinical diagnosis was exhibited: est. Achondroplasia. Sop. Pituitary hypoplasia. OSL. Growth retardation and skeletal development. S-shaped scoliosis of the spine. Dysplasia of both hips, thighs complicated dislocation on both sides. Patient was recommended to hormone replacement therapy: levothyroxine 50, genetically engineered growth hormone, and thyroid medications, calcium, vit D3. The patient was recommended consultation and treatment and also a podiatrist.
Conclusions
Patients with achondroplasia recommended MRI of the pituitary to identify possible hypo – or aplasia pituitary; 2) In the presence of hypopituitarism in patients with achondroplasia need appropriate hormone replacement therapy.

DOI: 10.1530/endoabs.37.EP1180

EP1181

Atypical teratoid rhabdoid tumor as a form of presentation of pituitary apoplexy

Maria Belen Ojeda-Schuldt, Laura Larrán-Escandón, Isabel Mateo-Gavira, Francisco Javier Vilchez-López, Inmaculada Gavilán-Villarejo & Manuel Aguilar-Diosdado
Department of Endocrinology, University Hospital Puerta del Mar, Cádiz, Spain.

Introduction
Even though pituitary apoplexy usually occurs in the context of a pituitary adenoma, it can also occur over other tumours, which is less common in adulthood and has faster growth and aggressiveness. It can also produce clinical, analytical and even radiological indications that are indistinguishable from a pituitary adenoma with ischemic and/or haemorrhagic events.
Case report
A 43-year-old female, with no medical history of interest except hypertension, had headaches for a period of 3 months, as well as vomiting, diplopia and left ptosis prior to admission. An image of a sellar pituitary tumour, measuring 20× 23 mm with suprasellar growth (with obliteration of the parasellar tank and cavernous sinus) compressing the optic chiasm was seen by magnetic resonance imaging confirming the presence of invasive pituitary macroadenoma with subacute bleeding. Analytical data showed hyponatremia and hypopituitarism with partial data. A tumour resection by transsphenoidal approach was perfomed, suspecting pituitary apoplexy. The hystopathological finding indicated rhabdoid tumour/teratoid atypical (WHO grade IV). The evolution was satisfactory until the ninth postoperative day when the patient started with a headache, vomiting and impaired level of consciousness. A CT scan was performed and confirmed a large isointense mass of about 7.2 cm in temporal and frontal rights lobes and suprasellar region, collapsing the right lateral ventricle. The patient finally died at 27 days after surgical intervention.
Conclusion
Teratoid/atypical rhabdoid tumor is an aggressive malignant tumour of the central nervous system that usually occurs in children younger than 3 years of age and has a poor prognosis despite chemotherapy and/or radiotherapy.

DOI: 10.1530/endoabs.37.EP1181

EP1182

17 α hydroxylase enzyme deficiency with hyperaldosteronism

Ilkay Kartal, Gonca Incemehmet Tamer & Hasan Hüseyin Mutlu
Medeniyet University, Goztepe Training and Research Hospital, Istanbul, Turkey.

Background
Congenital adrenal hyperplasia (CAH) resulting from 17 α hyroxylase enzyme deficiency (17OHD) is a rare autosomal recessive disorder. More than 150 cases were reported in the literature. Patients with 17OHD were reported to have hypoaldosteronism.
Case
A 16-year-old female referred to endocrinology outpatient clinic from family medicine department with the absence of a secondary sexual characteristics and primary amenorrhea. On physical examination she had no pubic or axillary hair. She has tanner stage I breast development and female external genitalia. Her height was 158 cm, weight 51 kg and blood pressure was 155/90 mm/Hg. Her karyotype was 46XX and bone age was nine years. Initial laboratory tests showed that serum glucose, urea, creatinin, sodium levels were normal; potassium level was low. Serum levels of 17 α hydroxyprogesterone (17-OHP), dehydroepiandosterone sulphate (DHEA-S), androstenodione, cortisol, plasma renin activity (PRA), oestradiol (E2) were low and serum aldosterone, adrenocorticotropic hormone (ACTH), deoxycorticosterone (DOC), luteinizing (LH), follicle stimulating hormone (FSH) was high (Table 1). All aldosterone and PRA values were obtained in upright position. Abdominal MRI showed rudimetary uterus and a nodullary development in the left adnexial area suggestive for ovary. The adrenal gland did not show significant adrenal hyperplasia and there was no mass lesion. Her blood pressure (110/80 mm/Hg) and potassium (3.9 mEg/l) became normal after beginning hydrocortisone tablet 10 mg in the morning, 10 mg at noon and 5 mg in the evening. Subsequently the patient was started on cyclic oestrogen for maturation of secondary sex characteristics. At the following visit we show that breast development was started but her blood pressure was 180/100 mm/Hg. Her potassium level was 3.4 meq/l we raised the total hydrocortisone dose to total 30 mg per day and added 25 mg sprinolactone. Few days later her self monitoring blood pressure results were between 160/100–140/90 mm/Hg. Amlodipin 10 mg was started. Few days later blood pressure became normal. At the last visit her blood pressure was 120/80 mm/Hg serum potassium (3.9 meq/l), aldosterone (194 pg/ml), PRA (0.762 ng/ml/h).

Table 1 Baseline biochemical and hormonal test results

Potassium (meq/l)	2.9	3.5–5.2
PRA upright (ng/ml/saat)	<0.2	0.2–6
Aldosteron upright (pg/ml)	385.45	20–220
ACTH 0800 h (pg/ml)	106	10–46
Cortisol 0800 h (μg/ml)	1.75	6.2–19.4
DHEA-S (μg/ml)	6.33	25–250
DOC (ng/dl)	250	4–12
17-OHP (ng/dl)	4.63	31–217
Total testosteron (ng/dl)	6.33	10–70
LH (mIU/ml)	34	follicular:2.12–10.89 luteal:1.20–12.86
FSH (mIU/ml)	89	follicular:3.85–8.78 luteal:1.79–5.12
E2 (pg/ml)	<20	follicular:27–122 luteal:49–291

Discussion
Patients with 17OHD have been reported to have hypoaldosteronism. We report a different variant of 17OHD with increased aldosteron and decreased renin production. We reviewed the literature and found at least 17 cases of 17OHD with normal aldosterone and 18 cases with elevated aldosterone levels.

The explanation for that is salt retaining due to volume expansion effects of the high concentrations of DOC, with consequent transcriptional down regulation of aldosterone synthase. The mechanism of normal and high aldosterone levels remains unclear. One explanation for this different aldosterone levels can be the cross reaction of the antisera for aldosterone measurement. Beckman Coulter radioimmunoassay kit was used for aldosterone measurement in this case.The antibody used in this kit is highly specific for aldosterone. According to the direction of use of this kit; low reactivities were obtained with several molecules (corticosterone, 18-OH corticosterone, etc). Patients who have been regulary exposed to animals or received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies that interfere with immunoassays; but there was no suspicion of having these antibodies in our patient. At the last visit her self-monitoring blood pressure results, serum potassium, aldosterone and PRA levels were all in normal limits as a result of hydrocortisone, sprinolactone, amlodipin treatment. We terminated cycling oestrogen use for four weeks before these tests because oestrogen, progesterone replacement may also interact with steroidogenesis. We thought that the radioimmunoassay in this study is reliable. Although the cross reaction possibility remains. Cases of 17OHD with hyperaldosteronism could be a variant of 17 OHD and could be genetically determined.

DOI: 10.1530/endoabs.37.EP1182

EP1183

Laryngeal carcinoma in acromegalic patients: a rare case

Gamze Akkus, Mehtap Evran, Murat Sert & Tamer Tetiker
Cukurova University, Adana, Turkey.

Introduction
Acromegaly is a very rare disease with persistent GH secretion due to excessive release of liver IGF1. The risk of malignancy, particularly colon cancer, is increased in acromegalic patients. But no evidence is found in the literature associated increasing of laryngeal carcinoma in acromegalic patients. We aimed to present this case that laryngeal carcinoma should be considered in acromegaly by the clinicians.
Case report
A 51-year-old male patient was diagnosed as acromegaly due to pituitary macroadenoma with the expansion of the suprasellar area localisation in flood. He was operated the right pterional craniotomy at December 2003. Postoperatively he was given the 28×200 cGy doses of radiotherapy linear treatment because of residual mass lesion in screening control MRI. He was medicated somatostatin analogues without cured by radiotherapy. In 2011, he admitted to our clinic with hoarseness and left ventrikuler mass extending was found by direct laryngoscopy. Polypoid soft tissue mass with narrowing the air column of the left vocal cord was detected by simultaneously neck CT. Biopsy revealed squamous cell carcinoma. Total laryngectomy with left lateral neck dissection was performed. Malignancy was not detected in PET CT which made of re-staging. Colonoscopy and endoscopy was performed and two polyps were found. As a result of pathology has been reported hyperplastic changes.
Conclusions
The elevated GH and IGF1 levels lead to a wide range of cardiovascular, respiratory diseases and malignancy also. A strong association between acromegaly and colon cancer and thyroid cancer has been highlighted. We could not find any data which acromegaly and in terms of laryngeal cancer association. However the laryngeal mucosa epitelium has been proven by the observational studies. We presented a case of a acromegaly patient who had a larynx carcinoma. Also clinicians should be aware that managing patients with acromegaly can occur other malignancy.

DOI: 10.1530/endoabs.37.EP1183

EP1184

Psychotropic medication – endocrine consequences

Georgiana Cristina Taujan, Diana Loreta Paun, Mihaela Nistor, Alina Maria Dumitru, Adina Simona Dragomir & Constantin Dumitrache
National Institute Of Endocrinology C.I.Parhon, Bucharest, Romania.

Given the increasing incidence in psychiatric pathology, adverse reactions of psychotropic medications, especially the metabolic and endocrine side effects, are encountered more frequently in clinical practice. We present the cases of two female patients with psychiatric pathology, in whom the specific treatment was accompanied by significant endocrine adverse reactions, making the tumoural differential diagnosis very difficult. The first case is of a patient aged 61 years, known with schizophrenia from the age of 27 years and treated for many years with valproic acid, who presented to our clinic for severe virilising syndrome, with a total serum testosterone of 9.2 ng/ml, rising the suspicion of ovarian or adrenal carcinoma. The second case is of a female patient aged 24 years, diagnosed with depressive disorder, in whom treatment with escitalopram and valproate was accompanied by amenorrhea-galactorrhoea syndrome and severe hyperprolactinaemia of 224 ng/ml (more specific for a macroprolactinoma). The pituitary CT scan revealed a microadenoma of 0.4/0.4 cm, generating important issues regarding differential diagnosis. Although endocrine side effects are often not life threatening and are less frequent than neurological side effects, such as sedation, extrapyramidal syndrome and anticholinergic disorders, recognising and correcting them is the key to successful therapy and ensures compliance of the patient with psychiatric pathology.

DOI: 10.1530/endoabs.37.EP1184

EP1185

Acromegaly due to McCune-Albright syndrome

Tatiana Borodich[1], Larisa Dzeranova[1], Ekaterina Pigarova[1], Zhanna Belaya[1], Elena Przhiyalkovskaya[1], Maxim Kutin[2], Alexander Vorontsov[1], Victoria Vladimirova[1], Elena Averkieva[1] & Liudmila Rozhinskaya[1]
[1]Endocrinology Research Centre, Moscow, Russia;
[2]Burdenko Neurosurgical Research Institute, Moscow, Russia.

A 27-year-old male patient during past 10 years noted a gradual change in his appearance, but began to seek a medical attention only 1.5 years ago due to reduced vision. Hormonal tests from March 2013 revealed marked elevation of GH to 106 mIU/ln (ref. values <20), and IGF1 to 567 ng/ml (121–336), decrease in testosterone levels to 1.91 ng/ml (3–12), with cortisol, LH, FSH, PRL, TSH values within the reference range; MRI of the brain showed a 4×7 mm adenoma of the anterior part of the pituitary, CT brain scan with contrast described poliostic dysplasia of the skull bones. From September 2013 octreotide depot injections therapy was initiated 10 mg per 28 days, with further increase to 20 mg per 28 days. In January 2014 levels of GH and IGF1 were still high in spite of medical treatment – 119 mIU/l and 1033 ng/ml respectively. In Apr 2014, at admission to Endocrinology Research Centre at the age of 27 years the patient was 205 cm tall and weighed 124 kg (BMI 29.5 kg/m^2). 'Café au lait' pigmentation of the skin was noted at the chest, back, and abdomen. His facial features were acromegaloid with sloped towered skull. Lab tests confirmed the presence of the active acromegaly (GH – 117 mIU/l, IGF1 – 1412 ng/ml), brain MRI with contrast showed a marked increase in the size of previously described adenoma (17×23×14 mm), and progression of the fibrous dysplasia (predominantly hypointense on T1) of the skull base, parietal, temporal bones, scales of the frontal and occipital bones, hypopneuma-tization of frontal sinus and ethmoidal labyrinth, narrowing of the internal and the external auditory canals on the left. All these symptoms allowed us to suspect a McCune-Albright (MAS) syndrome. The progressive clinical course of the disease, insensitivity to octreoride treatment was the basis for the choice of further surgical treatment despite the pronounced fibrous dysplasia of the skull base. In Oct 2014 at Burdenko Neurosurgical Research Institute the patient underwent endoscopic endonasal removal of tumor using navigation BrainLab. Postoperatively levels of GH and IGF1 decreased to – 27 mIU/l and 856 ng/ml, visual function had markedly improved. He was then followed on depo octreotide injections 30 mg per 28 days and cabergoline 2 mg per week with later dose adjustments.
Conclusions
The treatment of acromegaly in the setting of MAS is characterized by multiple challenges that require the participation of a team of experienced endocrinologists and neurosurgeons.
Disclosure
This work was supported by the Grant of the President of the Russian Federation (awarded to E G Przyjalkowski : grant Number: MK-5411.2014.7).

DOI: 10.1530/endoabs.37.EP1185

EP1186

Spontaneous pneumocephalus associated with a giant craniopharyngioma

Vasiliki Daraki[1], Efrosini Papadaki[2], Nikos Zampoulakis[1], Evangelia Mamalaki[1], George Kalikakis[1] & Stathis Papavasiliou[1]
[1]Department of Endocrinology, Diabetes and Metabolic Diseases, University Hospital of Crete., Heraklion, Greece; [2]Department of Radiology, University Hospital of Crete., Heraklion, Greece.

Introduction
Pneumocephalus is defined as the presence of air within the cranial cavity. It is usually associated with neurosurgical procedures but can also be caused by craniofacial trauma, infections and tumours of the skull base and rarely can occur spontaneously. Neoplasms involving the pituitary fossa are unusual causes of spontaneous pneumocephalus.
Case report
A 39-year-old man presented in the emergency department with significant visual loss, headache and rhinorrhoea. He had no previous history of head trauma or medical illnesses. He complained for increasing fatigue, headache and progressive loss of libido for the last 20 years. On physical examination his height was normal but he had low blood pressure and orthostasis. Optical field examination revealed preservation of central vision only. Initial laboratory examinations showed anaemia. All measured pituitary hormones were low except prolactin. The patient was diagnosed with panhypopituitarism. In the emergency department the patient brought with him a skull radiograph lateral view which showed air in the intracranial cavity. He underwent a brain MRI. A midline large space-occupying inhomogeneous mass was seen, extending and filling the suprasellar cistern, pituitary fossa and sphenoid sinus. It was characterised by cystic lesions separated by thin diaphragms and filling by fluid of increased signal intensity on T2 due to increased protein concentration. Haemorrhagic elements were demonstrated inside the solid contents at the left part of the mass. The aforementioned characteristics were indicative of a giant craniopharyngioma. The patient underwent neurosurgical debulking of the tumour and evacuation of the air collection. He was placed in replacement therapy with marked improvement Histological examination confirmed the diagnosis of craniopharyngioma.
Conclusion
Although extremely rare, spontaneous pneumocephalus should be considered as a possible diagnosis in patients with large pituitary lesions, rhinorrhoea and non-specific neurological manifestations. Early treatment of this potentially life-threatening disorder improves surveillance of these patients.

DOI: 10.1530/endoabs.37.EP1186

EP1187

Late diagnosis, early response - or the story of a smile

Roxana Novac & Nicoleta Rosu
Emergency Hospital, Moinesti, Romania.

We present the case of a 33-year-old male who addresses an endocrinology service for the first time in May 2014 for marked asthenia, drowsiness, muscular aches, and a delay in growing. The physiological exam showed difficulties in communicating and relation with the others based on his own negative image of himself, lack of self- trust, auto-isolation tendency, state of depression. We raised the suspicion of a panhypopitutarism confirmed by the lab exams that describe a somatotrope, tireotrope, corticotrope and gonadotrope deficit. The patient doesn't associate diabetes insipidus. In this conditions the patient associates a delay of bone age that is of approximately 14 years with a height at -1 S.D. for adult age (height velocity the last 2 years as declared was approximately 15 cm per year) and also a poor bone mass density z-score $= -1.8$. The IRM showed an empty sella. We initiated treatment with prednisolone on which the blood pressure raised till 110/70 mm/Hg, thyroid hormones and testosterone to complete his bone grow after which we will be placing him on growth hormone substitution for adults. After 6 months of treatment his general estate improved: his blood pressure raised, hair and skin improved, started puberty, but what was amazing were the changes in his emotional area, so the repeated physiological exam showed improved self-image, absence of depressive estates, increased capacity of communication, relating availability and most of all … the appearance of a smile.

DOI: 10.1530/endoabs.37.EP1187

EP1188

Ipilimumab-induced hypophysitis in cancer patients

Christian Lafuente[1], Karina Arcano[1], Fernando Guerrero[2], A Marengo[2], I Peiró[2], Ainara Soria[1], Juan José Diez[1], Carlos Villabona[2] & Pedro Iglesias[1]

Context
Ipilimumab is a human monoclonal antibody against cytotoxic T lymphocyte antigen-4 (CTLA-4), which enhances stimulation of cytotoxic T lymphocytes, resulting in an immune response against the tumour. This drug-induced hyperactivity of the immune system can lead to serious adverse effects including endocrine disorders such as autoimmune hypophysitis, thyroiditis and adrenal insufficiency.
Objective
To report our experience on ipilimumab-induced hypophysitis (IIH) in patients with advanced cancer.
Results
Four patients (three men (75%); aged 67.5 ± 8.7 years (range, 59–75)) with advanced cancer (three melanomas and one prostate cancer) were recruited. The clinical presentation of IIH was similar in all cases regardless of the underlying tumor. IHH developed after 12–19 weeks of starting treatment, usually between two and four ipilimumab cycles. Main symptoms were fatigue ($n=3$) and headache ($n=2$), nausea ($n=2$) and vomiting ($n=2$). IIH was associated with partial or total hypopituitarism in three cases. Pituitary hormone deficiencies most frequently affected were corticotrophin (ACTH, $n=3$), thyrotropin (TSH, $n=3$) and gonadotropins (FSH and LH, $n=3$). Two patients showed prolactin and growth hormone deficiencies. One patient did not develop any pituitary hormone deficiency although magnetic resonance imaging (MRI) of the pituitary showed morphologic changes of hypophysitis. MRI study showed enlarged pituitary in three patients. All patients were treated with high steroid doses ($>0,5$ mg/kg per day of prednisone or equivalent). After 28 months (range, 22.2–35.4) of follow-up, three patients remained with steroid hormone replacement therapy and two patients with replacement doses of levothyroxine. One patient recovered thyroid function.
Conclusion
IIH is an immune-related adverse event that can compromise the patient's life because of the possibility of development of adrenal and thyroid insufficiency in a high percentage of patients. Glucocorticoids are the treatment of choice. Hormone replacement therapy is indicated according to hormone deficiencies. Patients receiving immunomodulatory therapies should be closely monitored by baseline and follow-up hormone assessment.

DOI: 10.1530/endoabs.37.EP1188

EP1189

Abstract unavailable.

DOI: 10.1530/endoabs.37.EP1189

EP1190

A case report of two sibling with untreated congenital adrenal hyperplasia

Basak Karbek[1], Ayten Eraydın[2], Ozcan Ozbag[1] & Mesut Ozkaya[2]
[1]Gaziantep Doktor Ersin Arslan Hospital, Gaziantep, Turkey; [2]Medical Faculty, Gaziantep University, Gaziantep, Turkey.

Introduction
The term congenital adrenal hyperplasia (CAH) encompasses a group of autosomal recessive disorders, each of which involves a deficiency of an enzyme

involved in the synthesis of cortisol, aldosterone, or both. Deficiency of 21-hydroxylase, resulting from mutations or deletions of CYP21A, is the most common form of CAH, accounting for more than 90% of cases.
Case report
Two female siblings were referred to endocrine clinic with the complain of amenorrhea and hirsutism. İn their medical history; The elder sister presented to the paediatrics team at 4 years old with progressive enlargement of the clitoris, acne, muscular built and labioscrotal hyperpigmentation. There was no history of salt-losing crisis or hypoglycaemia. A diagnosis of CAH was made. The younger sister at 2 years old, presented with clitoral enlargement and acne. Similar investigations were performed and the diagnosis of CAH was confirmed. Both sisters were started on hydrocortisone upon diagnosis. Clitoral reduction and vaginal reconstruction surgery was performed for both sisters soon after the diagnosis. Although the seriousness of the illness was explained to their parents, replacement therapy were interrupted by them due to difficult social and economic status of the family, who lived for many years without basic medical care. 15 years later, at the age of 19 and 17; they were seen at the endocrine clinic. On physical examination, they were noted to have a short stature with body height of 1.48 and 1.52 cm. Physical examination revealed extreme virilisation. They were observed marked hirsutism, male type pubic hair, deepening of the voice, cliteromegaly, without breast development and primary amenorrhea. Hormonal analysis showed significantly elevated serum levels of 17-OHP (416, 513 nmol/l) and serum testosterone (30, 49 nmol/l). Mutational analysis of the CYP21A2 gene by multiplex ligation-dependent probe amplification and by polymerase chain reaction (PCR) followed by direct DNA sequencing showed homozygotes I172N mutation.
Discussion
Here we present two sisters with classic simple virilising form of 21-OHD with homozygotes I172N mutation diagnosed infancy who virilised after interruption of the glucocorticoid replacement therapy. If replacement therapy was discontinued, like our cases, there were serious consequences; risk of life, virilisation, change in psycho-social orientation.

DOI: 10.1530/endoabs.37.EP1190

EP1191

Phaeochromocytoma and Cushing syndrome: a rare association

Abdelkefi Cherifa, Haouat Emna, Kandara Hajer, Hbaili Nadia, Ben Salem Hachmi Leila & Ben Slama Claude
National Institute of Nutrition, Tunis, Tunisia.

Introduction
Phaeochromocytoma and Cushing syndrome are two uncommon endocrine conditions. The association of these two conditions is very rare and not well elucidated. We report an association of a phaeochromocytoma with an ACTH-dependant Cushing syndrome.
Case report
A 32-years-old female patient was admitted in the endocrine department for paroxysmal hypertension diagnosed in the immediate post partum period. She reported sweating and palpitation crises occurring with hypertensive peaks. Her blood pressure on treatment (calcic inhibitor and central antihypertensive) was 95/70. Clinical examination didn't reveal any evidence for Cushing syndrome. Laboratory findings showed hypokalaemia at 3.8 meq/l with a hyperkaliuresis. CT-scan revealed a 34×34 mm homogenous right adrenal mass. Urinary metanephrines were very high confirming phaeochromocytoma. Cortisol after low dose dexamethasone suppressing test (LDDST) was 60 nmol/l confirming the diagnosis of Cushing syndrome. ACTH was 39 ng/l and cortisol was suppressed by high dose dexamethasone test. Pituitary MRI was normal. The patient had an endoscopic adrenalectomy. Histology concluded to phaeochromocytoma. After surgery, hypertension and hypokaliaemia disappeared. Urinary metanephrines became normal and cortisol was suppressed by LDDST.
Conclusion
This is a rare case of phaeochromocytoma with a paraneoplasic ACTH secretion causing a subclinical Cushing syndrome.

DOI: 10.1530/endoabs.37.EP1191

EP1192

Coexistence of ovary tumour, congenital adrenal hyperplasia and triple translocation involving chromosome 9,11 and 12: Initial steps of defining new syndrome?

Sami Akbulut[1], Senay Arikan Durmaz[2], Timur Tuncali[3] & Nilgun Sogutcu[4]
[1]Department of Surgery, Diyarbakir Education and Research Hospital, Diyarbakir, Turkey; [2]Department of Endocrinology and Metabolism, Erzurum Region Education and Research Hospital, Erzurum, Turkey; [3]Faculty of Medicine, Department of Genetics, Ankara University, Ankara, Turkey; [4]Department of Pathology, Diyarbakir Education and Research Hospital, Diyarbakir, Turkey.

Introduction and aim
Congenital adrenal hyperplasia (CAH) is rare autosomal recessive disease. CAH due to 21-hydroxylase deficiency accounts for 95% of cases. We aim to define in this report 59-year-old woman with simple virilizing type CAH who diagnosed granulosa cell tumour and I172N mutation in the CYP21A as well as triple translocation involving chromosome 9p, 11p and 12p at first time in the literature.
Case report
A 59-year-old woman was applied to our clinic complained with abdominal pain and distension. She had irregular menstrual cycle per 3–4 month and hypomenorrhoea. She had gone through the menopause at 40 years old. She had never become pregnant. In physical examination her breast tissue had not developed and virilism was determined (modified Ferriman Galvey score >16). A palpable solid mass was detected in the right of abdomen. Ambiguous genitalia, clitoramegaly and hyperpigmentation were found. In computerized tomography giant ovarian mass in mesentery tissue was viewed. The mass (3500 g) was removed with the right tubo-ovarian structures. The granulosa cell tumour was diagnosed by the immunohistochemical examination. The high serum concentration of 17-OH progesteron measured at baseline and after 250-μg bolus of synthetic ACTH. In genetic analysis, we screened for six point mutations, large deletions, and noncommon mutations using restriction fragment length polymorphism (RFLP) methods, PCR, and sequencing of CYP21 gene respectively. The patient was detected to be homozygote for the I172N mutation. In addition, 50% of the metaphases examined had triple translocation (t(9; 11; 12)) between chromosomes 9p, 11p and 12p.
Conclusion
The I172N mutation in the CYP21A accompanied with t(9;11;12) translocation did not define previously in patients with CAH. This mutation may be sign of a new syndrome or a co-insidans that triggered to granulose cell tumour.

DOI: 10.1530/endoabs.37.EP1192

EP1193

Case report: an acromegalic patient presented with dysphagia

Feyzi Gokosmanoglu, Cigdem Tura Bahadir, Elif Kilic Kan & Aysegul Atmaca
Ondokuz Mayis University, Samsun, Turkey.

Introduction
Acromegaly is a chronic disease characterized by prognatism, frontal bossing, coarsened facial features, enlarged hands and feet due to overproduction of growth hormone (GH) generally by a pituitary adenoma. Here, we aimed to present an acromegalic patient presented with retropharyngeal hypertrophy first time in the literature.
Case report
65-year-old female patient had been referred to our department from otorhinolaryngology outpatient-clinic, where she had admitted with sensation of something stuck in throat for 2 years, upon finding overgrowth in uvula and orophayrngeal structures. She had symptoms of sweating, overgrowth in hands, feet, nose and lips. She had type 2 diabetes mellitus and hypertension history. Physical examination revealed coarsened facial features, deepened nasolabial folds, prognatism, tongue and oropharynx hypertrophy. Her blood glucose level was 173 mg/dl, IGF1 level was 929 ng/dl (normal range: 94–166 ng/dl) and GH level was 4.2 ng/dl. The lowest GH level during growth hormone suppression test was 3.8 ng/dl. Levels of other pituitary hormones were normal. Head and neck

magnetic resonance imaging (MRI) revealed expansion of orofacial bones and hyperthropy of the retropharyngeal soft tissue. MRI of pituitary gland revealed a 8×6 mm microadenoma with well defined boundaries in the pituitary gland. The patient was diagnosed with acromegaly and consulted with neurosurgery department regarding surgery.
Discussion
Acromegaly is a condition that should be considered in cases of soft tissue hyperthrophy in oral cavity, teeth occlusions, diastema and teeth prosthesis discrepancies.

DOI: 10.1530/endoabs.37.EP1193

EP1194

A rare case of adrenal histoplasmosis presenting as adrenal insufficiency and hypogonadism following a visit to bat caves

Gideon Mlawa[1], Mahesh Deore[2] & Saiji Nageshwaran[1]
[1]St Georges Hospital, London, UK; [2]Darrent Valley Hospital, Dartford, UK; [3]St Georges Hospital, London, UK.

Background
Histoplasmosis is an opportunistic fungal infection that commonly affects immunocompromised individuals. Histoplasmosis may be asymptomatic or may present with progressive systemic manifestations (pulmonary or disseminated). We present a case of a 76 year old immunocompetent man presented to hospital with 8 weeks history of general malaise and lethargy, intermittent night sweats, a productive cough, weight loss of 2.5 stones in two months and low grade fever. He had completed two courses of antibiotics with no resolution of his symptoms. He reported no history of tuberculosis contacts. Significant history was of travel to Malaysia and a visit to bat caves 2 years prior to the onset of symptoms. On admission, he was haemodynamically stable and his initial blood tests were normal apart from raised CRP of 80 mg/l. Chest XRay was normal.CT of sinuses showed minimal mucosal thickening. CT chest, abdomen and pelvis revealed large bilateral adrenal heterogeneous masses measuring 6.1×4.5×3.7 cm on the right, and 6.4×6.2×4.3 cm on the left. Adrenal biopsy showed fungal spores on microscopy. He was started on antifungal therapy for likely adrenal histoplasmosis and discharged home. He was readmitted 2 months later with a GCS of 6/15, Temperature 38 °C, and hypotensive episodes. He had normal CT and MRI brain results, negative blood cultures and unremarkable CSF studies. Echocardiogram excluded the vegetations. He was treated with intravenous empirical antibiotics and hydrocortisone. He was continued on his antifungal therapy. Initial short synacthen test showed normal response, however he became more tired and hyperpigmented with a subsequent short synacthen test showing a suboptimal response $T0 = 333$ nmol/l, $T30 = 378$ nmol/l. He also developed primary hypogonadism subsequently, thought to be due to effect of antifungals or due to histoplasmosis itself.
Conclusion
Adrenal histoplasmosis is rare, especially in immunocompetent individuals and should be considered as a differential diagnosis in any patient presenting with bilateral adrenal masses, constitutional symptoms and suggestive history. Also one should be vigilant about possible side effects of antifungals e.g. hypogonadism in this case.

DOI: 10.1530/endoabs.37.EP1194

EP1195

Differential diagnosis of low renin hypertension – pseudohypoaldosteronism type 2

Ieva Kalere[1,2], Ieva Tonne[1,2], Aivars Lejnieks[1,2] & Ilze Konrade[1,2]
[1]Riga East University Hospital, Riga, Latvia; [2]Riga Stradins University, Riga, Latvia.

Introduction
Pseudohypoaldosteronism type 2 (PHA2), also known as Gordon syndrome is a rare inherited form of low-renin hypertension associated with hyperkalaemia and hyperchloremic metabolic acidosis in patients with a normal glomerular filtration rate (GFR). PHA2 is the result of mutations in a family of serine-threonine kinases called with-no-lysine kinases (WNK) 1 and WNK4. These enzymes regulate electron channels in the aldosterone sensitive distal nephron, resulting in disrupted electron balance. PHA2 is a genetically and phenotypically heterogeneous entity, associated with high sensitivity to thiazides.
Case report
A 57 year old patient with anamnesis of treatment-naïve hypertension and *foramen ovale apertum* enclosed with occluder was admitted to the hospital for surgery due to adrenal mass – a typical adenoma found on abdominal CT 5 years ago with the diameter of 1.7 cm. Laboratory test results excluded Cushing syndrome, but primary hyperaldosteronism was not suspected due to persisting hyperkalaemia. Abdominal CT scan was repeated to evaluate the growth dynamics of the adrenal mass, revealing an enlarged left adrenal gland with a hypodense (9 HU) vascular mass 4.1 cm in diameter. Pre-operative testing revealed several laboratory abnormalities: hyperkalaemia 5.6 mmol/l (3.5–5.1) and hyperchloraemia 106 mmol/l (95–105), low plasma renin <0.5 μU/ml (4.4–46.1), normal aldosterone 95.8 pg/ml (25.2–392.0), normal GFR 100.5 ml/min, acidic urine pH 4.8 and decreased potassium excretion 23 mmol per day (25–125). Considering the findings of low renin hypertension with hyperkalaemia and normal GFR the diagnosis of PHA2 was established. The patient was started on antihypertensive treatment with thiazide diuretic and underwent left adrenalectomy. Histology conformed to hormonally inactive adrenocortical adenoma, Weiss score 2.
Conclusions
The current case demonstrates the challenges of differential diagnosis of low renin hypertension depicting the characteristic findings of PHA2. It should be noted that upon correct diagnosis this form of low renin hypertension is easily treatable with thiazide diuretics.

DOI: 10.1530/endoabs.37.EP1195

EP1196

The hidden liquorice: apparent mineralocorticoid excess caused by inadvertent exposure to liquorice root extract

Ailsa Maria Main & Ulla Feldt-Rasmussen
Faculty of Health Sciences, University of Endocrinology, Rigshospitalet, and University of Copenhagen, Copenhagen, Denmark.

Introduction
Excessive consumption of liquorice can cause endocrine symptoms of apparent mineralocorticoid excess (AME). This is usually caused by excessive consumption of liquorice-containing sweets and native liquorice root but the different chemical compounds in liquorice may also be used in many other products where it is considered an additive and therefore not explicitly declared.
Case
We here report a 21-year-old patient who exhibited severe symptoms of AME (oedema, spells of dizziness, headaches and peripheral paraesthesia as well as general and muscular fatigue) due to inadvertent excessive intake of liquorice. Blood samples showed low serum potassium (2.3–3.1 mmol/l, ref (3.5–4.6)) requiring potassium supplementation (40 mmol×2 daily) and high normal sodium (142–147 mmol/l, ref (137–145)). Measurement of 24 h urinary steroid metabolite excretion raised the suspicion of AME. Additional blood tests showed undetectable serum concentrations of aldosterone (<38 pmol/l, ref (50–360)) and renin ($<2*10^{-3}$ IU/l, ref (6–60)). Pituitary function (thyroid hormones, prolactin, IGF1, IGFBP3) was normal. No obvious endocrine cause of AME could be established and the patient re-evaluated all personal dietary products. Liquorice root was present in several herbal teas and sugar-free chewing gum that had been consumed daily in large amounts. Cessation of usage of these products resulted in complete recovery of AME-related symptoms.
Conclusions
Our case report revealed other potential sources of liquorice than sweets including industrial sweeteners and flavouring agents that could potentially cause clinical symptoms. Clinicians should thus extend their medical history to a broader range of consumer products when suspecting AME.

DOI: 10.1530/endoabs.37.EP1196

EP1197

From erectile dysfunction to brain subependymoma: a case report

Tatjana Bacun[1,2], Aleksandar Kibel[1,3], Dunja Degmecic[4,5], Karin Zibar[6,7] & Roman Pavic[8,9]
[1]University Hospital Centre Osijek, Internal Medicine Clinic, Osijek, Croatia; [2]Faculty of Medicine, Department of Internal Medicine, University of Osijek, Osijek, Croatia; [3]Faculty of Medicine, Department of Physiology and Immunology, University of Osijek, Osijek, Croatia; [4]University Hospital Centre Osijek, Clinic of Psychiatry, Osijek, Croatia; [5]Faculty of Medicine, Department of Psychiatry, University of Osijek, Osijek, Croatia; [6]University Clinic Vuk Vrhovac, Zagreb, Croatia, [7]University Hospital Merkur, Zagreb, Croatia; [8]University Hospital of Traumatology, Zagreb, Croatia; [9]Faculty of Medicine, Department of Surgery, University of Osijek, Osijek, Croatia.

Introduction
Endocrinopathies are rare causes of erectile dysfunction and previously cases of hyperprolactinaemia and pituitary adenomas have been reported.
Case report
We present the clinical case of a 27-year old male, married for 4 years with no children, presented with possible infertility and erectile dysfunction which was previously interpreted as caused by a poor social and psychological situation in the family. After additional endocrinological (mildly elevated prolactin levels and reduced levels of testosterone) and radiological (skull X-ray, CT scan and MRI) an underlying subependymoma was discovered. The subependymoma was expanding in the sellar and suprasellar regions and pressing against the pituitary gland. The patient experienced occasional periorbital and temporal headaches, loss of appetite, general weakness. A Goldman perimeter test was consistent with bitemporal hemianopia. The resulting endocrine disorder caused the problems which were subjectively at first mainly manifested as erectile dysfunction. The patient underwent a left-sided supraorbital craniotomy and complete surgical removal of the tumor at the Department of Neurosurgery. The histopathology findings described a subependymoma (G II). One year after surgery, the patient was in good general condition, but with bitemporal hemianopia, with atrophy of the right optic nerve and complete loss of vision in his right eye, panhypopituitarism and impotence. Two years later, with hormone replacement therapy (desmopressin, hydrocortisone, levothyroxine, testosterone undecanoate) there was no sexual dysfunction.
Conclusions
The case is an educative example about the necessity to keep possible intracranial lesions in mind when starting the workup of a patient presenting with erectile dysfunction. It may be of broad clinical interest not only for endocrinologists, but for practitioners in various fields.

DOI: 10.1530/endoabs.37.EP1197

EP1198

Intestinal obstruction and bowel perforation as a presenting feature of a phaeochromocytoma

Izaskun Olaizola[1], Estela Elias[2], Ana Maria Chacon[1], Ismene Bilbao[1], Nerea Egaña[1], Cristina Garcia[1], Maite Aranburu[1], Tomas Matteucci[2], Alfredo Yoldi[1] & Miguel Goena[1]
[1]Hospital Universitario Donostia, Donostia San Sebastián, Gipuzkoa, Spain; [2]Hospital Bidasoa, Irún, Gipuzkoa, Spain.

Introduction
Phaeocromocytomas are a rare catecholamine secreting tumours that can present in multiple ways. The classic triad of symptoms consists of episodic headache, sweating, and tachycardia. Most patients do not have the three classic symptoms. Sustained or paroxysmal hypertension is the most common sign. Among less common symptoms and signs constipation has been described and few cases of megacolon and phaeochromocytoma have been published.
Case report
A 39 year-old man, with previous medical history of schizophrenia, autism and pulmonary tuberculosis with a partial left lobectomy, complained of abdominal pain of 3 days. An abdominal X-ray demonstrated dilated loops of small and large bowel with air-fluid levels in the upright position, abundant faecal remainders in the large bowel and faecaloma. Large bowel obstruction was suspected presenting an unfavorable evolution despite medical treatment. CT scan showed small and large bowel obstruction secondary to an intestinal malrotation with signs of sigmoid colon and rectum suffering and a left adrenal incidentaloma of 6 cm. An urgent surgical intervention was performed showing small bowel obstruction secondary to internal hernia secondary to dolichomegasigma and large bowel perforation with loculated abscess, performing sigmoidectomy, terminal colostomy and abscess exeresis. The postoperative evolution was good. The functionality of the adrenal incidentaloma was studied showing urinary metanephrines consistent with phaeochromocytoma. Treatment with phenoxybenzamine was started and left adrenalectomy was performed confirming the diagnosis of phaeochromocytoma. 1 year after the surgery he has not presented new episodes of bowel obstruction.
Conclusions
Intestinal obstruction is an important clinical condition that can present in association of phaeochromocytoma. Due to the risk of intervention in a patient previously not treated with alpha-blockade, if an adrenal incidentaloma is observed in a patient with intestinal obstruction, phaeochromocytoma should be ruled out in order to prevent. surgery complications.

DOI: 10.1530/endoabs.37.EP1198

EP1199

Spontaneous resolution of bilateral avascular necrosis of the femoral head following cure of Cushing's syndrome secondary to primary pigmented micronodular adrenal disease

Agnieszka Pazderska[1], Stephen Crowther[2], Pradeep Govender[3], Kevin C Conlon[4,6], James Gibney[1] & Mark Sherlock[1,5]
[1]Department of Endocrinology, Adelaide and Meath Hospitals, incorporating the National Children's Hospital, Tallaght, Dublin 24, Ireland; [2]Department of Pathology, Adelaide and Meath Hospitals, incorporating the National Children's Hospital, Tallaght, Dublin 24, Ireland; [3]Department of Radiology, Adelaide and Meath Hospitals, incorporating the National Children's Hospital, Tallaght, Dublin 24, Ireland; [4]Professorial Surgical Unit, Adelaide and Meath Hospitals, incorporating the National Children's Hospital, Tallaght, Dublin 24, Ireland; [5]Department of Endocrinology, Trinity College Dublin, Dublin, Ireland; [6]Department of Surgery, Trinity College Dublin, Dublin, Ireland.

Avascular necrosis is a rare presenting feature of endogenous hypercortisolism. The literature suggests that, if left untreated, complete collapse of the femoral head may ensue, necessitating hip replacement in up to 70% of patients. The majority of described patients with avascular necrosis due to endogenous hypercortisolaemia were treated surgically.
Case report
A 36-year-old female, investigated for right leg pain, reported rapid weight gain, easy bruising and secondary amenorrhea. She had abdominal adiposity with violaceous striae, facial plethora and hirsutism, atrophic skin, ecchymosis and proximal muscle weakness. Spinal imaging showed L4/L5 disc herniation, fractures of L1 and multiple ribs. Investigations confirmed cortisol excess (cortisol post low dose 48-h dexamethasone suppression test 807 nmol/l; 24-h urinary free cortisol 1443 nmol (normal $<$290 nmol)). ACTH was $<$5.0 pg/ml. CT demonstrated subtle left adrenal gland hypertrophy. Post left adrenalectomy hypercortisolaemia persisted. Histology revealed primary pigmented micronodular adrenal disease. Post-operatively right leg pain worsened and left leg pain developed, affecting mobility. MRI showed bilateral femoral head avascular necrosis, which was not surgically treated at this point. She underwent right adrenalectomy and commenced steroid replacement. Within 4 months of surgery her leg pain resolved and she could ambulate freely. Repeat MRI showed marked improvement in high signal intensity in both femoral heads, consistent with spontaneous healing of avascular necrosis.
Conclusion
We report a case of a 36-year-old woman with Cushing's syndrome due to primary pigmented nodular adrenocortical disease, presenting with symptomatic avascular necrosis of both hips. This was managed conservatively from an orthopaedic perspective. Following cure of hypercortisolaemia, the patient experienced an excellent functional and radiological recovery. She remains symptom-free 4 years post adrenalectomy. This case is the first to report a favourable outcome over long-term follow up of a patient with bilateral avascular necrosis of the hip which reversed with treatment of endogenous hypercortisolaemia.

DOI: 10.1530/endoabs.37.EP1199

EP1200

New onset Graves' disease as a cause of an adrenal crisis in an unrecognised empty sella

Hela Marmouch[1,2], Tasnim Slim[1], Fadia Boubaker[1], Sondes Arfa[1], Hanene Sayadi[1,2], Manel Jmal[1,2] & Ines Khochtali[1,2]
[1]Department of Internal Medecine-Endocrinology, MONASTIR, Tunisia; [2]Faculty of Medecine, MONASTIR, Tunisia.

Introduction
A 66-year-old woman was admitted as an emergency with vomiting, hypotension and serum cortisol of 0.92 microg/dl indicative of adrenal failure. She was found to be hyperthyroid (fT_4 = 72 pmol/l).
Case report
She had hypotension (blood pressure 80/40 mm/Hg) She was fit and well till the age of 65. Endocrine assessment revealed deficiency in ACTH-cortisol, growth hormone, and gonadotropin, as well as low-normal fT_4. On the day of his emergency admission he looked ill and dehydrated, though was fully conscious and cooperative. Heart rate was 110 beats/min (sinus rhythm), blood pressure 85/60 mm/Hg. There were no obvious features of infection, but there was marked tremor and thyroid bruit. She received treatment with intravenous fluids and hydrocortisone. Administration of large dose of methimazole (40 mg per day)

resulted in gradual decrease in fT_4. Pituitary MRI showed empty sella. The patient was found to have increased titre of antithyroperoxidase (anti-TPO) and anti-TSH receptor (anti-TSHR) antibodies (2100 IU/l (ref. range <40) and 3.7 IU/l (ref. range <1.0), respectively). She was referred for radioactive iodine treatment. Iodine uptake scan performed prior to radioiodine administration confirmed uniformly increased iodine uptake consistent with Graves' disease.
Discussion
We encountered a patient with unrecognised adrenocortical disease due to empty sella, in whom development of Graves' hyperthyroidism caused an adrenal crisis. Empty sella syndrome in this case can be related to autoimmune hypophysitis.
Conclusion
Our case illustrates coexistence of hypopituitarism and clinically significant autoimmune thyroid disease. The presence of hypopituitarism does not preclude the development of autoimmune thyrotoxicosis.

DOI: 10.1530/endoabs.37.EP1200

EP1201

Klinefelter syndrome with portal vein aneurysm: case report

Isilay Kalan Sari[1], Ramazan Cosar[2], Sevda Yilmaz[3] & Hüseyin Demirci[4]
[1]Department of Endocrinology and Metabolic Diseases, Burdur State Hospital, Burdur, Turkey; [2]Faculty of Medicine, Department of Internal Medicine, Kirikkale University, Kirikkale, Turkey; [3]Faculty of Medicine, Department of Radiology, Kirikkale University, Kirikkale, Turkey; [4]Faculty of Medicine, Department of Endocrinology and Metabolic Diseases, Turgut Özal University, Ankara, Turkey.

Introduction
Klinefelter syndrome (KS) is the most common chromosomal disorder characterized by clinical features of hypogonadism and infertility. Portal vein aneurysms are very rare clinic findings. Reported cases are increasing due to use of modern imaging techniques in clinic practise.
Case report
19-year-old man was admitted to our hospital with complaints of abdominal pain, nausea, and vomiting associated with eating. He was recently diagnosed with KS by chromosomal analysis, which was performed because of eunucoid appearance and gynecomastia. On physical examination, lungs were clear and heart beats were regular. No abdominal tenderness was found and no enlarged liver or spleen was palpated. Laboratory studies revealed: white blood cell counts, 6.600 mm^3; haemoglobin, 14.6 g/dl; AST, 18 U/l, ALT, 9 U/l; GGT 20 U/l; ALP 111 U/L; amylase 40 U/l; total bilirubin 1.47 mg/dl; FSH 52.62 mIU/ml; LH 23.11 mIU/ml; total testosterone 3.28 ng/ml; oestradiol 21.59 pg/ml. An abdominal ultrasound scan showed 23 mm anechoic, saccular expansion in the left branch of portal vein. There were no features of thrombosis, portal hypertension, chronic liver disease, pancreatic mass or pancreatitis. No aneurysmal change was noted in arterial tree and there were no pathological findings in other intraabdominal organs. Monophasic, turbulent venous flow was detected in aneurysmal dilatation by Doppler ultrasonography. Esophagogastroduodenoscopy was performed and revealed pangastritis. Abdominal pain was attributed to gastritis.
Conclusion
Portal vein aneurysms are rare presences and are usually asymptomatic. Portal vein thrombosis is a severe complication of PVA and can result in intestinal ischemia or intestinal infarction. Early diagnosis and initiation of therapy is important. It is well known that KS is associated with an increased risk of venous thrombosis include portal vein thrombosis. So, it is important to follow up the patient for the risk of portal vein thrombosis. For asymptomatic patients regular clinic follow-up will be sufficient.

DOI: 10.1530/endoabs.37.EP1201

EP1202

Exaggerated cortisol response in heterozygous carriers with a mutation in the melanocortin-2 receptor (MC2R) gene

Ma Pyeh Kyithar[1], Andrew Green[2], Claire Hughes[3], Nuala Murphy[4] & Maria Byrne[1]
[1]Endocrinology Department, Mater Misericordiae University Hospital, Dublin, Ireland; [2]National Centre for Medical Genetics, Our Lady's Hospital, Crumlin, Dublin, Ireland; [3]Barts and the London School of Medicine, London, UK; [4]Children's University Hospital, Dublin, Ireland.

Introduction
Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive disease characterised by ACTH resistance and isolated glucocorticoid deficiency. Mutations of ACTH receptor, known as melanocortin-2 receptor (MC2R), and melanocortin-2 receptor accessory protein (MRAP) account for approximately 25 and 15 to 20% of cases respectively. To date there is no strong evidence that heterozygous carriers have abnormal cortisol secretion.
Case
We studied a pedigree with a MC2R mutation where the index case presented with severe hypoglycaemia at three years of age in 1970s and was subsequently diagnosed with adrenal insufficiency. Of eight siblings, two brothers died as neonates, with hindsight due to adrenal insufficiency and a third brother was diagnosed with adrenal insufficiency when he presented comatose at two months and remained profoundly handicapped and later died. The index case was found to have a homozygous missense mutation c.221G$>$T, leading to p.S74I (substitution of serine with isoleucine at position 74) in the MC2R gene. We studied three of her siblings with the heterozygous S74I mutation in the MC2R gene. The mean age of heterozygous carriers was 31.3 ± 2.5 years. They had generalised slightly tanned skin, but no significant hyperpigmentation. They were normotensive and had no symptoms suggestive of glucocorticoid deficiency. Short synacthen testing with 250 µg tetracosactide in heterozygous carriers showed baseline ACTH levels of 53.7 ± 31.9 ng/l (normal range <46 ng/l), 0 min cortisol levels of 506 ± 168 nmol/l, 30 min cortisol levels of 952 ± 85 nmol/l, and 60 min cortisol levels of 953 ± 36 nmol/l.
Conclusion
The study of heterozygous MC2R mutation carriers demonstrated slightly elevated baseline ACTH levels with a relatively high baseline cortisol level and an exaggerated cortisol response to synacthen test. These findings suggest there is no evidence of glucocorticoid deficiency despite elevated ACTH levels in heterozygous carriers with MC2R mutations.

DOI: 10.1530/endoabs.37.EP1202

EP1203

Pituitary enlargement in pregnancy presenting with visual field defects and interesting imaging

Hsiu Lye Yap, Maura Moriarty, Edouard Mills, Ana Pokrajac & Thomas Galliford
West Hertfordshire Hospitals NHS Trust, West Hertfordshire, UK.

We report a rare case of a patient presenting with headaches and almost complete bilateral hemianopia during her third trimester of pregnancy. This lady presented with headaches and vomiting 2 years prior, with a pituitary MRI initially reporting an acute pituitary haemorrhage. This time, due to progression of her visual field defects, it was decided in a multidisciplinary meeting to perform a Caesarean section at 37 weeks and start Cabergoline post-operatively, as the patient did not plan to breast-feed. She had a raised prolactin in keeping with pregnancy, but the rest of her pituitary profile was normal. Upon reviewing her initial pituitary MRI and subsequent imaging at a later date, it was noted that the patient had a bulky pituitary gland, but the signal characteristics on MRI remained unchanged, which brought the original diagnosis of pituitary haemorrhage into question. It was therefore felt that this was either a proteinaceous developmental cyst or persisting blood products on serial imaging. This pituitary abnormality in combination with physiological pituitary gland enlargement in pregnancy is likely to have caused chiasmal compromise and visual field defects in this patient. Since her delivery, she has had repeat MRI imaging, which showed regression in the size of her pituitary gland with no compression of the optic chiasm. She was gradually weaned off the cabergoline. There is no evidence of any endocrine dysfunction. However, the patient still reports some persisting visual defects, which are unaccounted for in view of her most recent pituitary imaging. She has been referred on for neuro-ophthalmic assessment. This case also demonstrates the importance of multi-specialty management in a complex patient to achieve a satisfactory outcome. The patient has been strongly advised to avoid future pregnancies, as it is likely that she will get chiasmal compression once again.

DOI: 10.1530/endoabs.37.EP1203

EP1204

Familial SDHC mutation associated with prolactin/gh-secreting pituitary adenoma and paraganglioma

Mohammed Barigou[1], Alexandre Buffet[1,2], Antoine Bennet[1], Pascal Pigny[3], Laurent Bellec[4], Philippe Caron & Delphine Vezzosi[1]
[1]Department of Endocrinology, Metabolic Diseases and Nutrition, CHU Larrey, Toulouse, France; [2]INSERM UMR 970, Centre de recherche Cardiovasculaire à l'HEGP, Paris, France; [3]Centre de Biologie-Pathologie du CHRU de Lille, Lille, France; [4]Urology Department, CHU Rangueil-Toulouse, Toulouse, France.

Introduction
SDH genes mutations are associated with hereditary phaeochromocytoma and paraganglioma syndromes. We describe the case of a patient with SDHC related familial paraganglioma and pituitary adenoma.
Case
A 65-year old man consulted for an incidentally discovered 7 cm abdominal mass on CT-scan, lateral to the right kidney, invading inferior vena cava, associated to a retroperitoneal adenomegaly and a lesion on the body of L2 vertebra with spinal MRI aspect of metastasis. All these lesions showed hypermetabolism on 18F-FDG PET. Continuous blood pressure monitoring, plasma catecholamines and their methoxylated metabolites were normal. Chromogranine A was four times normal (Normal range <100 µg/l). Total right adrenalectomy, lumbo-aortic lymphadenectomy and nephrectomy were performed. Vertebral metastasis was treated by radiofrequency. Histopathology of the primary tumor confirmed the diagnosis of paraganglioma with 2% mitotic index. During follow-up, erectile dysfunction developed. Endocrine evaluation revealed partial hypogonadotropic hypogonadism (testosterone 214 ng/dl Normal: (280–820), LH 2.2 mUI/ml, FSH 2.5 mUI/ml) with hyperprolactinaemia (470 ng/ml, normal value <19 ng/ml) and elevated IGF1 level (214 ng/ml, normal: 41–196 ng/ml). OGTT confirmed GH hypersecretion. MRI showed a T_2 hyperintense pituitary adenoma of $15\times$ 17 mm with left cavernous sinus extension without optic compression. We retained the diagnosis of PRL/GH-secreting pituitary adenoma and started dopamine agonist plus somatostatin analogue treatment. Genetic analysis revealed an new mutation on SDHC gene on exon 4 c239-242dupGTGC. The same mutation was found in his siblings (son, daughter and the grandson). His son had a non-secreting pituitary microadenoma, without pituitary abnormalities in the daughter. Work-up for paraganglioma was negative in siblings.
Conclusion
This case suggests that SDHC gene mutations could be related to pituitary adenomas occurrence in association with paraganglioma syndromes, but more studies should be conducted to define the pathogenic pathways of this relationship.

DOI: 10.1530/endoabs.37.EP1204

EP1205

Bilaterally slipped capital femoral epiphysis in growth hormone–deficient patient: osteosynthesis also needs the oestrogen epiphyseal fusion- case report

Dragan Tesic[1], Milena Mitrovic[1], Jovan Vlaski[2], Svetozar Damjanovic[3] & Vera Popovic[3]
[1]Clinic for Endocrinology, Diabetes and Metabolic Disturbances, Novi Sad, Serbia; [2]Department of Pediatrics, Novi Sad, Serbia; [3]Institute for Endocrinology, Belgrade, Serbia.

Introduction
Growth without growth hormone is seen also in patient with craniopharyngioma. We just speculate what anabolic factors might be involved in this process. However, oestrogen through its receptors lead to epiphyseal fusion. In this case report we would like to present the patient with bilateral slipped femoral epiphysis (SFE) and interventions made at tertiary health care level.
Case report
20-years-old female, operated from craniopharyngioma when was 10 year, bogy height 167 cm, body weight 71.8 kg, not regularly on levothyroxine 50 gr, in December 2013 presented as pain in right hip, on X-ray SFE, and osteosynthesis was performed. In July 2013 similar clinical picture but on left side. Patient was sended at tertiary level. After multislice CT scanning same surgical procedure performed on left femur with three screws. Then patient was moved on endocrinology department. Clinically, according to sex characteristics, patient was Tanner I stage, without measurable values of growth hormone, insulin like growth factor I, gonadotropins and estrogens, insulinaemia 17.3 mU/l, blood glucose 4.5 mmol/l. On X-ray of the left hand skeletal age was 12 year. Estrogen therapy started with 0. mg etinil estradiol and after 5 months increased on 2 mg estradiol, 21 and 7 days pause. Skeletal age at 5 m, 10 m and 13 were 13 years 6 months, 14 year, 15–16 year respectively. Increased markers of bone resorption (cross laps) returned back into normal range. DEXA scan of lumbar spine was improved from – 3.2 T-score onto – 2.8 in just 6 month period. Body height was changed from 167.5 cm to on 171 cm and body weight from 67.5–80 kg.
Conclusions
After the operation of craniopharyngioma and growth without growth hormone we have to follow skeletal growth and on time introduce sex hormones. Later, in young adults we have to consider a small dosages of growth hormone to improve their body composition.

DOI: 10.1530/endoabs.37.EP1205

EP1206

Effectiveness of octoreotide administration before surgery for GH-TSH co-secreting pituitary adenoma with thyrotoxicosis: a case report

Shihori Kimura[1], Osamu Isozaki[1], Izumi Fukuda[1], Satoshi Morimoto[1], Yasufumi Seki[1], Kaoru Yamashita[1], Noriyoshi Takano[1], Akiko Otsuki[1], Terumi Kaneshige[1], Kanako Bokuda[1], Daisuke Watanabe[1], Takashi Ando[1], Naomi Hizuka[1], Kosaku Amano[2], Takashi Komori[3], Yoshikazu Okada[2] & Atsuhiro Ichihara[1]
[1]Department of Medicine II, Tokyo Women's Medical University, Tokyo, Japan; [2]Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan; [3]Department of Pathology I, Tokyo Women's Medical University, Tokyo, Japan.

Introduction
TSH-secreting pituitary adenoma (TSHoma) sometimes brings on rare cause of hyperthyroidism because of its excessive TSH secretion. Though the first line of treatment for TSHoma is surgical removal of tumour, hyperthyroidism often causes perioperative thyroid storm. Here, we report a case of GH-TSH pituitary adenoma whose thyrotoxicosis was controlled by 5 days' octoreotide (OCT) subcutaneous administration before surgery.
Case report
A 47-year-old woman with hyperhidrosis and palpitation for these 7 years was admitted to our hospital. She also presented acromegalic change, such as the increase in size of finger rings and shoes. In endocrinological examination, serum levels of TSH, fT_4 and fT_3 were 1.500 µU/ml, 3.73 ng/dl and 8.06 pg/ml, and l GH and IGF1 were 10.31 ng/ml and 861 ng/ml. 75gOGTT did not suppress GH (nadir GH: 10.26 ng/ml). MRI demonstrated a pituitary adenoma of $18\times12\times$ 9 mm. GH-TSH co-secreting pituitary adenoma was suspected, and in order to prevent from perioperative thyroid storm, we scheduled OCT administration. Single OCT administration (50 µg) decreased serum TSH levels from 1.740 to 0.515 µU/ml and GH levels from 11.42 to 0.68 ng/dl respectively. Then, OCT (100 µg/day) was injected additionally for 5 days and serum fT_4, fT_3 and IGF1 levels decreased to 1.53 ng/dl, 2.65 pg/ml, and 350 ng/ml respectively before operation. Pituitary adenoma was completely and uneventfully removed *via* trans-sphenoidal-surgery and her all hormone levels were normalized without any medication.
Conclusion
A case of GH TSH co-secreting pituitary adenoma with thyrotoxicosis was reported. To prevent from perioperative thyroid storm, OCT administration should be recommended.

DOI: 10.1530/endoabs.37.EP1206

EP1207

Cushing's syndrome secondary to aberrant hormone receptors in a patient with macronodular adrenal hyperplasia ACTH-independent

María Molina Vega, Jose Antonio Lopez Medina, Araceli Muñoz Garach, Isabel Cornejo Pareja, Cristina Díaz Perdigones, Ana Gómez Pérez & Francisco Tinahones Madueño
Hospital Universitario Virgen de la Victoria, Malaga, Spain.

Introduction
Cushing's syndrome (CS) due to macronodular adrenal hyperplasia ACTH-independent (MAHAI) is rare. Regulation of cortisol secretion by G-protein-coupled receptors (GPCRs) aberrantly expressed is frequently found in MAHAI. Various aberrant receptors have been reported, mostly: GIP, vasopressin, beta-adrenergic, LH/hCG and serotonin.
Case report
61 years old woman. Medical history: type 2 diabetes, hypertension, obesity, dyslipidaemia and severe sleep apnoea. Treatment: metformin, insulin, lyxisenatide, *irbesartan-hydrochlorothiazide, torasemide, diltiazem, acetyl salicylic acid and atorvastatin.* Physical examination: moon face, centripetal obesity, abdominal striaes and thin extremities. Laboratory evaluation: HbA_{1c} 8.4%, TSH 2.06 μIU/ml, serum cortisol: at 0800 h:17.2 μg/dl (5–25), overnight dexamethasone suppression (1 mg): 5.3 μg/dl, after 0.5 mg dexamethasone every 6 h for 48 h suppression: 5.03 μg/dl, after nocturnal 8 mg dexamethasone suppression: 5.7 μg/dl. Urinary free cortisol repeatedly normal (49.4 and 24 μg per day), salivary cortisol repeatedly raised (0.382 and 0.292 ng/ml). ACTH 2.83, others adrenal hormonal profile normal. With these findings, the suspected diagnosis was Cushing's syndrome. CT: adrenal glands enlarged with homogeneous hypodense nodules (3.3×2.6 cm right; 3.2×1.9 cm left). Because of the known association between MAHAI and aberrant GPCRs some tests were performed: posture test, standard mixed meal, LHRH (100 mg i.v.), metroclopramide (10 mg orally), glucagon (1 mg i.v.) and AVP (10 IU i.m.). Positive response (50% increase in plasma cortisol levels) in the standard mixed test and metroclopramide test (indicating serotonin and GIP aberrant receptors). Right adrenalectomy is planned.
Conclusion
In patients with MAHAI aberrant GPCRs can be identified. The detection of such aberrant receptors is necessary in all patients with MAHAI. Identification of these receptors can provide specific pharmacological treatment with or without adrenalectomy.

DOI: 10.1530/endoabs.37.EP1207

EP1208

Complicated investigation of adrenal incidentaloma in a critically ill patient – a case study

Simona Kratochvílová[1], Petr Wohl[1], Lenka Hošková[2], Jirí Kettner[2], Jana Vrbská[2], Michal Kudla[3] & Jana Brunová[1]
[1]Institute for Clinical and Experimental Medicine, Diabetes Centre, Prague, Czech Republic; [2]Cardiology Department, Institute for Clinical and Experimental Medicine, Prague, Czech Republic;[3]Transplant Surgery Department, Institute for Clinical and Experimental Medicine, Prague, Czech Republic.

Adrenal incidentaloma is frequently encountered in endocrinological praxis, however in specific situations the proper investigation is almost impossible. A 60-years old patient was admitted to our intensive care unit with a myocardial infarction in cardiogenic shock requiring ionotropic support and intraaortic balloon counterpulsation. On account of ejection fraction 15–20% an urgent pretransplantation investigation was started. Abdominal ultrasound displayed a hypoechogenic structure 35×30 mm in the left suprarenal region and adrenal CT confirmed a low density mass 25×37 mm. Both aldosterone (886.8 ng/l) and plasmatic renin activity (PRA) (5.9 ng/ml/hod) were highly elevated but our patient was treated with interfering medication (furosemide and spironolactone). Plasma metanephrine levels were within normal limits despite of catecholamine support. The patient had no cushingoid features and ACTH level was normal, but dexametahsone test was falsely positive due to hyperactivation of stress axis and inadequate absorption of dexamethasone. When excluding phaeochomocytoma and malignancy the patient was indicated to urgent heart transplantation. 2 months after the operation, in patient already having normal cardiac function, hypertension and the tendency to hypokalaemia occurred. Elevated aldosterone and supressed PRA were detected. We confirmed the diagnosis of primary hyperaldosteronism by the saline infusion test: basal PRA 0.448 ug/l/hod and aldosterone 182 ng/l; supressed PRA 0.486 ug/l/hod; aldosterone 363 ng/l, the ratio aldosterone/PRA 40 (ng/dl/ng/ml/hod). We did not perform the renal veins cannulation because of the chronic immunosuppressive corticosteroid administration. Left adrenalectomy with histological evidence of adenoma resulted in normalization of blood pressure and potassium levels 6 months after the heart transplantation. An excessive secondary activation of the renin-angiotensin-aldosterone axis in the patient with severe heart failure completely superimposed the original primary hyperaldosteronism pattern.
Disclosure
Supported by the Ministry of Health of the Czech Republic (MZO 00023001).

DOI: 10.1530/endoabs.37.EP1208

EP1209

An underactive hypothalamo-pituitary-adrenal axis in a shift worker with chronic fatigue syndrome

Ljiljana Marina, Svetlana Vujovic, Miomira Ivovic, Milina Tancic-Gajic, Zorana Arizanovic, Dragana Rakovic, Milos Zarkovic, Tijana Lalic, Marina Nikolic-Djurovic, Zvezdana Jemuovic & Dragan Micic
Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia.

Introduction
Chronic fatigue syndrome is characterised by a state of chronic fatigue that persists for more than 6 months and has no clear cause.
Case report
A 38-year-old male was referred to our Clinic due to chronic fatigue, unrefreshing sleep, substantial impairment in concentration, headaches and postexertional malaise lasting from 6 to 9 months for 9 years. As a mechanical engineer he was working in shifts 12 h day/24 h break/12 h night/72 h break for 9 years. Other than allergy to penicillin he denied any significant health issues. Complete blood count, liver and kidney function tests, basal gonadotropin, TSH, prolactin, ACTH, cortisol and testosterone levels were normal. Hepatitis B, C, HIV and anti nuclear antibodies were negative. Chest X-ray and abdominal ultrasound were normal. Psychiatrist excluded a psychiatric disorder. Standard and 1 μg Synacthen test showed inadequate peak cortisol 419 and 532 nmol/l respectively. Insulin tolerance test, with hypoglycaemia of 1.2 mmol/l in 30', showed inadequate peak responses of ACTH 25 ng/l in 30', cortisol 345 nmol/l in 60', prolactin 282 mIU/l and low normal growth hormone 22 mIU/l in 60'. Endocranium with hypothalamo-pituitary region MRI was normal. The patient was diagnosed with chronic fatigue syndrome (CFS). As we advised he stopped working in shifts and commenced a low-grade physical activity with cognitive – behavioural therapy. After 6 months he was complaint free with adequate cortisol levels in standard and 1 μg Synacthen test, 718 and 715 nmol/l respectively. After a year he was still complaint free with basal cortisol 570 nmol/l.
Conclusion
The cause of CFS in our patient was the long-term exposure to a stressor – shift work, which led to a circadian disruption, crashing adaptive mechanisms and leading to a disease.

DOI: 10.1530/endoabs.37.EP1209

EP1210

A case of pleomorphic adenoma and acromegaly: a coincidence or a pathophysiological association?

Oya Topaloglu[1], Sefika Burcak Polat[2], Cemaleddin Oztürk[3], Murat Bavbek[4], Togay Muderris[5], Reyhan Ersoy[1] & Bekir Cakir
[1]Faculty of Medicine, Department of Endocrinology and Metabolism, Yildirim Beyazit University, Ankara, Turkey; [2]Department of Endocrinology and Metabolism, Atatürk Education and Research Hospital, Ankara, Turkey; [3]Department of Internal Medicine, Atatürk Education and Research Hospital, Ankara, Turkey; [4]Faculty of Medicine, Department of Brain Surgery, Yildirim Beyazit University, Ankara, Turkey; [5]Department of Otorhinolaryngology, Atatürk Education and Research Hospital, Ankara, Turkey.

Introduction
Acromegaly is a chronic disease caused by excessive secretion of growth hormone (GH), and as a result, of insulin-like growth factor-1 (IGF1). Although controversial, frequency of both benign and malignant neoplasm formation is thought to be increased in acromegalic patients. Pleomorphic adenoma is the most

common arising tumour from the parotid salivary gland. Here we report the case of a 33-year-old woman with acromegaly and also who presented with a swelling on the left neck and diagnosed as pleomorphic adenoma arising from parotid gland after excision of the tumour.
Case report
33-year-old woman admitted to the hospital complaining of a 2-week history of visual loss and headache. She also determined weight gain, menstrual irregularity, libido loss, galactorrhoea, and a slowly growing swelling on the left neck during the last year. Hypophyseal MRI revealed a mass of 20×32 mm occupying the sellae and invasing right cavernous sisternae and extending to the optic chiasm. Hormonal evaluation demonstrated that the patient had acromegaly and secondary hypothyroidism. Parotid ultrasound (US) revealed a 42×28×45 mm heterogenous, hypoechoic intraglandular lobulated solid mass occupying left parotid gland superficial lobe and extending to the deep lobe. Hypohpyseal adenoma was excised by transsphenoidal route and immunohistochemical analysis showed extensive GH positivity. She had residual tumour after the operation and somatostatin analogous therapy was started in the follow-up period. After eight months from the hypophyseal operation the parotid tumour was excised and pathology showed that it was a pleomorphic adenoma.
Conclusion
It seems that this is the first case of a coincidence between an acromegaly and pleomorphic adenoma of parotid gland in the English literature. We don't have still enough knowledge about an association between salivary gland tumours and acromegaly. If present or not this association must be evaluated with the further studies.

DOI: 10.1530/endoabs.37.EP1210

EP1211

Primary hyperaldosteronism: case presentation

Rodica Petris[1], Constantin Dumitrache[1], Sorin Paun[2], Catalina Poiana[1], Roxana Ganescu[2], Mara Carsote[1] & Diana Paun[1]
[1]National Institute of Endocrinology C.I. Parhon, Bucharest, Romania; [2]Emergency Hospital Bucharest Floreasca, Bucharest, Romania.

Introduction
We should consider testing for primary aldosteronism in the presence of hypertension and hypokalaemia, resistant hypertension, onset of hypertension at a young age (<20 year), severe hypertension and whenever considering secondary hypertension.
Case report
We presented the case of a 38 years old woman who was admitted in the National Institute of Endocrinology C.I. Parhon Bucharest for the evaluation of high blood pressure. She has high blood pressure for 10 years (maximum value 190/100 mm/Hg) and she is on β blocker and angiotensin II receptor blockers. She has no other medical history and her blood pressure is still 150/80 mm/Hg on the antihypertensive drugs. She has heredocolateral antecedents of high blood pressure (her mother). After she has stopped for 4 weeks the antihypertensive drugs, we detected hypopotasemia (K: 2.9 nmol/l), normal serum natrium, and normal biochemia but high levels of serum aldosterone (121 ng/ml) and low levels of serum renin (2 μUI/ml) with plasma metanephrines and normetanephrines in the upper normal range and normal plasma cortisol with good response after 1 mg overnight dexamethasone suppression test. An adrenal computed tomography has been performed and we discovered a left adrenal mass of 1.2/0.9 cm. We have replaced the β blocker with Spironolactona (200 mg per day) and Aspacardin and on these medications she has high normal blood pressure and normal potassemia. The patient was transferred to the surgery where they performed laparoscopic adrenalectomy. 2 weeks after surgery she has normal blood pressure and normal natraemia and potassemia without medications.
conclusion
We presented the case of woman with primary hyperaldosteronism and although she has high blood pressure for 10 years and we have not expected that it would be entiraly coreccted after surgery, patient did not need any antihypertensive drugs after surgery.

DOI: 10.1530/endoabs.37.EP1211

EP1212

Hyperprolactinaemia and breast abscess: is there a link?

Imen Rojbi, Emna Haouat, Hajer Kandara, Basma Saada, Leila Ben Salem Hachmi & Claude Ben Slama
National Institute of Nutrition, Tunis, Tunisia.

Introduction
Hyperprolactinemia is a common endocrine condition causing galactorrhoea. Breast abscess is a frequent complication of the post partum period and breast feeding but it rarely occurs out of these two situations. We report the case of a patient presenting with tumoural hyperprolactinaemia associated with a breast abscess.
Case report
A 34 years-old patient presented with galactorrhoea, spaniomenorrhoea and headache for six months. She had nothing special in her medical history and was not on drugs. She was the mother of two children aged eight and four. Prolactine assessment was made twice and confirmed the hyperprolactinaemia (Prolactine: 94 and 110 ng/ml). Pituitary MRI concluded to a pituitary microadenoma so that microprolactinoma was diagnosed and the patient put on dopaminergic agonists. 15 days later, the patient suddenly developed a painful mass of the left breast. Biologic assessment showed an inflammatory syndrome with hyperleucocytosis. The breast ultrasound examination revealed an abscess of 4 cm in the superior external quadrant, with no other abnormalities of the breast. The course of the abscess was good on antibiotics (Amoxicillin + clavulanic acid) and surgery was not indicated.
Conclusion
This case report highlights the fact that during pathological hyperprolactinaemia, the histology of the breast glands may be modified leading to a risk of developing breast abscess. This phenomenon is may be exactly the same than during breastfeeding. No other similar cases have been reported in the literature.

DOI: 10.1530/endoabs.37.EP1212

EP1213

5 years complete clinical remission after single adrenalectomy for severe occult ACTH-dependent Cushing's syndrome

Daniel Grigorie[1,2], Andra Caragheorgheopol[1], Dan Hortopan[1] & Alina Sucaliuc[1,2]
[1]National Institute of Endocrinology, Bucharest, Romania; [2]Carol Davila University of Medicine, Bucharest, Romania.

Introduction
Complete long-term clinical remission in occult ectopic ACTH syndrome after a single adrenalectomy is unexpected.
Case report
5 year ago, a 54-year-old man was admitted because of resistant HTA, multiple severe vertebral fractures, muscle weakness and cushingoid features of at least 1 year. Adrenal tests were diagnostic of ACTH-dependent Cushing'syndrome: ACTH = 263 pg/ml, high plasma (62 μg/dl) and urinary free cortisol (UFC = 1256 μg per day) with no suppression after both low-dose (cortisol = 40.12 μg/dl; UFC = 255.36 μg per day) and high-dose dexamethasone (cortisol = 32.95 μg/dl; UFC = 1193.2 μg per day). A pituitary MRI showed no identifiable tumour. CTs of the thorax and abdomen and a ^{18}-FDG-PET CT scan failed to identify a possible tumour. A right adrenal laparoscopic adrenalectomy was performed. 1 mo postsurgery ACTH decreased to 79.8 pg/ml and cortisol was 16.7 μg/dl, non-suppressible with low dose DXM (7.37 μg/dl); low testosterone, 25OHD normalised, and bone turnover markers increased significantly (osteocalcin 10 ×). As clinical improvement was significant the patient declined the second adrenalectomy. 10 mo postsurgery all cushingoid features disappeared and the patient was in very good clinical condition with mild HTA and normal blood chemistries as he is now. Adrenal tests were performed annually: they fluctuated, with serum cortisol/UFC normal or high normal but nonsuppressible (or paradoxically increased); ACTH also was around 100 pg/ml. BMD increased progressively for 5 year (32% at the FN). 2 years ago a CT scan revealed a small pulmonary nodule (10 mm) but a SMS (^{111}-indium-pentetreotide) scan was negative; the nodule was stable on recent CT. We wait for the patient consent to operate the pulmonary nodule.
Conclusion
The case shows an unexpected rapid and complete clinical remission of a severe occult ectopic Cushing' syndrome. The abnormal cortisol feed-back persisted for the duration of follow-up.

DOI: 10.1530/endoabs.37.EP1213

EP1214

Aberrant expression of serotonin receptors in an aldosterone- and cortisol-producing adenoma

Maria Lytrivi[1], Denis Brisbois[1], Bernard Corvilain[1], Pieter Demetter[1], Camilo Garcia[3], Valerio Lucidi[1], Rodrigo Moreno-Reyes[1], Stella Vudu[1], Celine Duparc[2], Julien Wils[2], Herve Lefebvre[2], Estelle Louiset[2] & Natacha Driessens[1]
[1]Erasme University Hospital, Brussels, Belgium; [2]INSERM, U982, University of Rouen, Mont-Saint-Aignan, France; [3]Jules Bordet Institut, Brussels, Belgium.

Introduction
Aberrant expression of serotonin receptors has been described to be involved in the pathophysiology of both aldosterone-producing and cortisol-producing adrenal adenomas.
Case report
A 46-year-old woman was referred for evaluation of severe hypertension associated with hypokalaemia. Primary aldosteronism with concurrent subclinical Cushing's syndrome was diagnosed. A CT-scan identified a lesion of 4 cm in the right adrenal gland and a second lesion of 1 cm in the left adrenal gland, both displaying benign imaging phenotype. Following dexamethasone suppression, we explored the potential aberrant expression of serotonin receptors in the adrenal cortex by intravenous administration of metoclopramide, a serotonin type 4 receptor (5-HT_4-R) agonist. This led to abnormal cortisol increase and physiological response of aldosterone in peripheral blood. Adrenal venous sampling was then performed in basal conditions and after metoclopramide stimulation. An increase in cortisol level was observed in the left adrenal vein after stimulation. ^{131}I-19-Iodocholesterol scintigraphy showed intense radiotracer uptake in the right adrenal mass and weak uptake in the contralateral mass. Right laparoscopic adrenalectomy was performed. Histological examination revealed an adrenocortical adenoma. *In vitro*, cultured adrenocortical cells derived from the tumoural tissue exhibited aldosterone and cortisol co-secretion. Administration of 5-HT or metoclopramide to the cells induced a dose-dependent increase in cortisol production. These effects were inhibited by concomitant administration of the 5-HT_4-R antagonist GR113808. Incubation of tumour tissue fragments with 5-HT induced a significant increase in aldosterone production which was abrogated in the presence of GR113808. These data were suggestive of aberrant expression of 5HT_4-R in the tumoural tissue.
Conclusion
We report a rare case of an aldosterone- and cortisol-co-producing adenoma in a patient with severe hypertension and bilateral adrenal masses exhibiting an abnormal plasma cortisol response to metoclopramide. *In vitro* studies revealed enhanced sensitivity of the tumour tissue to 5-HT indicative of illicit expression of 5-HT_4 receptors.

DOI: 10.1530/endoabs.37.EP1214

EP1215

'Idiopathic'- the truly unknown or yet another hiding place for autoimmunity? A case of central diabetes insipidus in a young woman with Hashimoto thyroiditis

Alexandra Nila[1], Cristina Serbanescu[1], Mihaela Epure[1], Minodora Betivoiu[1], Sorina Martin[1,2] & Simona Fica[1,2]
[1]Endocrinology Department, Bucharest, Elias Emergency Hospital, Romania; [2]Endocrinology Department, Carol Davila University of Medicine and Pharmacology, Bucharest, Romania.

Introduction
Central diabetes insipidus is a rare, chronic disease characterized by polyuria and polydipsia due to a partial or total vasopressin deficiency (hypothalamic – neurohypophysial system damage). The aetiology can be familial (autosomal dominant inheritance, X-linked recessive traits; mutation of the vasopressin – neurophysin II genes), secondary (tumours, infections, infiltrative diseases, trauma, vascular lesions) and idiopathic (10–30%).
Case report
We present the case of a 24 year-old female who presented in our clinic for a polydipsia- polyuria syndrome (10 l per day) with a sudden onset 3 months prior her admission. She had a family history of Hashimoto thyroiditis and Diabetes Mellitus type 1, and a personal history of Hashimoto thyroiditis with hypothyroidism for which she had been taking treatment with L-thyroxine for almost 1 year. Physical examination: overweight (BMI 28 kg/m^2), blood pressure 120/95 mm/Hg, heart rate 108 bpm, no signs or symptoms of pulmonary disease. She had no modifications in circadian rhythm or appetite, normal menstrual cycle, no history of head trauma, pregnancy or childbirth. Lab tests: routine investigations and inflammatory markers were normal, endocrinological testing revealed a normal anterior pituitary function and a balanced hypothyroidism substitution (TSH = 3.01 μIU/ml, fT_4 = 1.47 ng/dl). The water deprivation test and ADH value when the test ended (< 1 ng/l) were suggestive for central diabetes insipidus. Hypothalamic-pituitary MRI with contrast showed no pathological modifications except for the absence of the physiological posterior pituitary bright spot. The patient received long-term oral desmopressin treatment and her fluid intake and output normalised.
Conclusion
Central Diabetes Insipidus is rare chronic disease, even rarer in the case of young adults. When no familial or secondary cause of vasopressin deficiency is feasible, vascular lesions and autoimmune processes must be taken in consideration before labelling it as 'idiopathic'. In this particular case, given the personal and familial history of autoimmune diseases, despite the non-suggestive MRI findings, anti-pituitary and vasopressin-cell autoantibodies should be determined as an attempt to look even further and truly define a diagnosis.

DOI: 10.1530/endoabs.37.EP1215

EP1216

ARMC5 mutation in a family with Cushing syndrome due to bilateral macronodular adrenal hyperplasia

Teresa Rego[1], Fernando Fonseca[1], Ana Agapito[1], Stéphanie Espiard[2], Karine Perlemoine[2] & Jérôme Bertherat[2]
[1]Endocrinology Department, Curry Cabral Hospital, Lisbon, Portugal; [2]Endocrinology Department, Hôpital Cochin, Paris, France.

Introduction
Bilateral macronodular adrenal hyperplasia (BMAH) is a rare aetiology of Cushing syndrome. Familial clustering suggests a genetic cause that was recently confirmed, after identification of inactivating germline mutations in *armadillo repeat containing 5* (ARMC5) gene.
Clinical case
A 70 years old female admitted due to femoral neck fracture in May 2014, presented central obesity, rubeosis and hypertension. Laboratory work up revealed: ACTH < 5 pg/ml; urinary free cortisol (UFC) – 532 ug per day (ref.v. – 20–90); serum cortisol after DST – 21 ug/dl; Abdominal MRI: enlarged nodular adrenals (right – 55 × 54 × 30 mm; left – 85 × 53 × 35 mm). She was submitted to bilateral adrenalectomy and histology confirmed cortical nodular hyperplasia (adrenal weight: right – 62 g; left – 151 g). In 2006 this patient's 39 years old daughter had been observed by one of the authors. She presented severe clinical hypercortisolism and ACTH < 5 pg/ml; UFC – 204 ug per day; serum cortisol after DST – 16.2 ug/dl; Abdominal CT scan showed bilateral enlarged nodular adrenals with maximal axis of 15 cm for both. Bilateral adrenalectomy was performed (adrenal weight: right – 68 g; left – 104 g) and pathology revealed cortical nodular hyperplasia. In this familial context of severe bilateral disease, genetic study was preformed. Leucocyte DNA genotyping identified in both patients a ARMC5 mutation in exon 1 c.172_173insA p.158Nfs*44.
Comments
The clinical cases herein described have an identical phenotype with severe hypercortisolism and huge adrenal glands, but different ages on diagnosis. Current knowledge of inheritance of this disease, its insidious nature and the well known deleterious effect of hypercortisolism favour genetic study of other family members. Since ARMC5, a tumoral supressor gene, is expressed in many organs and recent findings suggest an association of BMAH and meningeoma, a watchful follow-up is required.

DOI: 10.1530/endoabs.37.EP1216

EP1217

Successful pregnancy outcome in recurrent phaeochromocytoma: a clinical case report

Evelina Praneviciene[1], Birute Zilaitiene[2,3], Lina Barsiene[3], Lina Radzeviciene[2,3], Tomas Birzietis[4] & Rasa Verkauskiene[2,3]
[1]Faculty of Medicine, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania; [2]Institute of Endocrinology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania; [3]Department of Endocrinology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania; [4]Department of Obstetrics and Gynaecology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania.

Introduction
Phaeochromocytoma in pregnancy is very rare and potentially dangerous situation for mother and foetus. Failure to diagnose this condition or suboptimal management can be disastrous for mother and/or foetus, because of raised catecholamine levels.
Case
A 22-year-old pregnant woman (8 weeks' gestation) with hypertension and a suspected recurrence of phaeochromocytoma was referred to the Endocrinology Department in March 2014. The pregnancy was unplanned. In physical examination her height – 176 cm, weight – 74 kg, blood pressure and pulse were 156/90 mmHg and 92 beats/min respectively. Laboratory investigations: metanephrin 0.42 nmol/l (0–0.456), normetanephrin >16.38 nmol/l (0–0.1037), potassium 3.4 mmol/l (3.8–5.3), plasma renin activity (PRA) 16.81 ng/l (1.6–14.7), aldosterone (ALD) 633 ng/l (35–300), with normal ALD:PRA ratio, chromogranin A 361.18 μg/l (0–100). From her medical history it was already known that she underwent right adrenalectomy due to pheochromocytoma in March 2012. 6 months later increased blood preassure till 160/100 mmHg was observed. On abdominal CT scan (June 2013) – right adrenal gland removed, several $\sim 1.1 \times 1.0$ cm lymph nodes are visible, left adrenal gland structural, without any additional masses in it. Metanephrin and normetanephrin tests indicated significantly elevated catecholamines levels. Unfortunately abdominal MRI (August 2013, September 2014) and MIBG scans (October 2013, February 2014) did not reveal possible source of catecholamines hyperproduction as well. Genetic testing results were negative. Hypertention during first trimester was treated with Labetalol 600mg/day, Metildopa 1000 mg per day, potassium chloride 1500 mg per day. Phenoxybenzamine hydrochloride was added later on and titrated till 100 mg per day in order to reach satisfactory blood pressure control. In September 2014 the patient had uncomplicated delivery of a healthy boy (weight – 2890 g, height – 47 cm, Apgar score 9–9) *via* Caesarean section. She is breast-feeding and continues Labetalol 900 mg per day for hypertension control. Further investigations are planned to identify localization of phaeochromocytoma.
Conclusion
This case illustrates that adequate medical management in the case of phaeochromocytoma predispose the successful pregnancy outcome.

DOI: 10.1530/endoabs.37.EP1217

EP1218

Rare aetiology for primary adrenal failure: ACTH resistance

Ioana Hristov[2], Simona Gherasim[2], Ana Hreniuc[2], Maria Christina Ungureanu[1,2], Cristina Preda[1,2], Carmen Vulpoi[1,2], Voichita Mogos[1,2] & Letitia Leustean[1,2]
[1]University of Medicine and Pharmacy 'Gr.T.Popa', Iasi, Romania; [2]Universitary Hospital St Spiridon, Iasi, Romania.

Introduction
ACTH resistance syndromes are rare, autosomal and genetically heterogeneous diseases that include familial glucocorticoid deficiency and triple A syndrome. These are characterised by early onset of primary adrenocortical insufficiency associated with hypoglycaemia, convulsions and skin pigmentation.
Case report
We present the case of primary adrenal failure in a boy diagnosed at the age of four, during a decompensation episode with hypoglycaemia and hyponatremic convulsive episode. Adrenal functional evaluation revealed: low cortisol with suboptimal ACTH response-Synacthen (cortisol T60 = 17.6 ng/dl) and very high ACTH >1500 pg/ml. Glucocorticoid and mineralocorticoid treatment improved the clinical and biologic status (normal natremia and glycaemia). The aetiological evaluation for this adrenal insufficiency included: negative anti-adrenal antibodies, normal long chain fatty acids, negative tuberculosis testing, normal 17-OH progesterone and normal pituitary (MRI) and normal adrenal aspect (CT). This profile suggests a possible diagnosis of ACTH resistance syndrome. Molecular analysis for the ACTH receptor gene (MC2R) and its associated protein (MRAP) is needed for confirming this diagnosis. Clinical aspect is particular: no skin hyperpigmentation (high ACTH >1500)-suggesting a possible melanocyte receptor deficiency (MC1-R). This ACTH resistance diagnosis seems to be associated with alacrima (Shirmer test confirmed low lacrimal secretion) but no achalasia symptoms were objectified.
Discussion
Several mutations have been found to affect the ACTH-R gene and results in different effects on receptor function. Given the ACTH resistance on multiple receptor locations: MC1-R, MC2-R (adrenal insufficiency, absence of hyper pigmentation) we suspect a co-factor mutation. Molecular analysis of DNA for MC2R, MRAP, and AAAS genes in literature shows that about 50% of FGD has unknown genetic cause. Recently, it was shown that MC2R interacts with Nup50, a nuclear pore complex protein, suggesting that this interaction could be a novel mechanism of action of ACTH receptor.

DOI: 10.1530/endoabs.37.EP1218

EP1219

Autoimmune hypophysitis: from pituitary expansion to empty sella: description of four cases

Giulia Marconcini[1], Isabella Lupi[1], Luca Manetti[1], Mirco Cosottini[2], Claudio Urbani[1], Enio Martino[1], Claudio Marcocci[1] & Fausto Bogazzi[1]
[1]Department of Experimental Medicine, University of Pisa, Pisa, Italy; [2]Department of Neuroscience, University of Pisa, Pisa, Italy.

Four patients with autoimmune hypophysitis were followed since the diagnosis of the disease. All presented with severe headache, decreased libido, astenia. Case 1 and 3 presented polyuria and polydipsia. At MRI pituitary was enlarged, with high gadolinum uptake and stalk enlargement.
Case 1, male 41 years. MRI volume: AP 13 mm, CC 7 mm. Hormonal assessment: central hypothyroidism, hypoadrenalism, hypogonadism, normal GH and IGF1, hyperprolactinemia, central diabetes insipidus. Pituitary biopsy: severe lymphomonocitic infiltrate. Case 2, male 54 years. MRI volume: AP 13.5 mm, CC 7.7 mm. Hormonal assessment: central hypothyroidism, hypoadrenalism, hypogonadism, GH deficiency, hyperprolactinemia. Case 3, male 74 years. MRI volume: AP 9 mm, CC 7 mm. Hormonal assessment: panhypopituitarism, central diabetes insipidus. Pituitary biopsy: rich IgG4 lymphomonocitic infiltration. Case 4, female 35 years. MRI volume: AP 16 mm, CC 7 mm. Hormonal assessment: panhypopituitarism, hyperprolactinemia. All patients were treated by oral prednisone therapy (starting dose: 40 mg/day gradually tapered over 6 months) and followed with regular hormonal exams and pituitary MRI. At the last outpatient visit: Case 1 (6 years AR): recovery of gonadic and thyroid function, GH deficiency, adrenal insufficiency and diabetes insipidus remained unchanged. MRI: shrinked pituitary (AP 8 mm, CC 4 mm). Case 2 (1 year AR): complete recovery of adrenal function, persistence of hypogonadism and GH deficiency, subclinical hypopthyroidism. MRI: shrinked pituitary (AP 11 mm, CC 2.5 mm). Case 3 (6 years AR) persistence of panhypopituitarism and diabetes insipidus. MRI: shrinked pituitary (AP 6 mm, CC 4 mm). Case 4 (1 year AR) complete recovery of pituitary function. MRI: normal pituitary volume (AP 12 mm, CC 4 mm).
Conclusion
Glucocorticoid treatment is effective in improving pituitary function and pituitary mass. Over the years new hormonal defects may appear along with pituitary shrinkage: empty sella might be the outcome of autoimmune hypohysitis. (abbreviations: AR, after remission; AP, antero–posterior diameter; CC, cranio-caudal diameter).

DOI: 10.1530/endoabs.37.EP1219

EP1220

Occurrence of liver failure in post-surgery hypopituitaric patients

Valentina Lo Preiato, Danilo Ribichini, Margherita Baccini, Renato Pasquali & Uberto Pagotto
Endocrinology Unit, Sant'Orsola-Malpighi Hospital, Alma Mater University, Bologna, Italy.

Multiple pituitary hormone deficit and hypothalamic obesity are common complications after brain surgery for childhood tumors. Despite adequate replacement hormone therapy, obesity develops equally, but liver failure is not usually described. In this study, four subjects who had undergone surgery for brain tumors involving the peri-hypothalamic area when they were nursing or as youths (9 months, 6 years, 9 years and 20 years). They were referred to our Unit when they were 19, 23, 23 and 31 years old, respectively. One of this patients had a pilocytic astrocytoma, two of these patients had a craniopharyngioma, and the last a third ventricle germinoma. One patient underwent radiotherapy and

chemotherapy after surgery and another one received four transphenoidal or transcranial surgical operations. All patients developed panhypopituitarism, but only two had taken in childhood and adolescent age adequate hormone replacement therapies since brain damage. Since the other two patients came to our observation, adequate hormonal replacement therapy was proposed. All patients developed obesity (BMI 39.2–46.6 kg/m^2) or overweight (BMI: 27.1). The two patients adequately treated for hypopituitarism after surgery, developed a fatty liver when they were 16 and 21 years old respectively. In both cases, steatosis progressively evolved into cirrhosis after 2 years. One of these patients also developed a hepatic-pulmonary syndrome and underwent liver transplant at the age of 25 years. In the two patients with inadequate or absent hormone replacement therapy, a diagnosis of cirrhosis was concomitant with the first appropriate endocrinological care during hospitalization for liver failure. The analysis of these four cases shows that pediatric peri-hypothalamic surgery may be associated with very severe hepatic clinical features, induced by mechanisms not yet known, regardless of hormone replacement therapy. It is therefore very important to start a careful follow-up of these patients from childhood for early detection of possible liver failure.

DOI: 10.1530/endoabs.37.EP1220

EP1221

Two treatment patterns of thyrotropinomas with over 3-year follow-up

Mihail Coculescu & Madalina Vintila
Carol Davila University of Medicine and Pharmacy, Bucharest, Romania.

Introduction
Thyrotropinomas are rare pituitary tumours. Neurosurgery is considered the first-line treatment, followed by medical therapy with somatostatin analogues or radiotherapy.
Case reports
We present two cases of thyrotropinomas with different therapeutic approaches. Case 1: A 63-year old man presented with severe thyrotoxicosis. Biochemical evaluation showed inappropriate TSH secretion (TSH = 7.5 mU/l, FT_4 = 45.5 pmol/l); computed tomography revealed a pituitary macroadenoma (2.37/2.56 cm). The patient underwent preoperative lanreotide and antithyroid drugs preparation before trans-sphenoidal tumour removal. Immunohistochemistry showed a pure thyrotropinoma. After neurosurgery, he had complete disease remission without any antithyroid medication and no signs of recurrence after 7-year follow-up. However, he developed postoperative gonadotropin deficiency. Case 2: A man, 36-years, with total thyroidectomy for thyroid follicular adenoma presented with high TSH (15 mU/l) although he received daily 100 μg of levothyroxine and serum thyroid hormones were in high-normal concentrations (total T_4 = 11 μg/dl). Adding T_3 (20–30 μg/day) to T_4 treatment, TSH was still high (between 41 and 18.4 mU/l for FT_4 between 1.28 and 2 ng/dl), showing inadequate TSH secretion. Pituitary MRI revealed a 1.62/1.45/1.6 cm mass. Acute octreotide test showed decreasing of TSH from 22.4 to 0.53 μU/ml with no change in serum T_4 and T_3 levels. The patient refused surgery and received chronic treatment with long-acting octreotide, 20 mg/month. Along 3-year follow-up he had good biochemical response (TSH between 4.35 and 2.87 mU/ml while normal T_4 and T_3 levels under substitution) and ~25% reduction of tumor dimensions (1.21/0.92/1.29 cm). Whenever octreotide was stopped, inappropriate TSH secretion relapsed.
Conclusions
Neurosurgery is the treatment of choice in thyrotropinomas but when surgery is refused somatostatin analogues are an efficient alternative for long-time disease control.
Disclosure
This work received financial support through the project entitled 'CERO – Career profile: Romanian Researcher', grant number POSDRU/159/1.5/S/135760, cofinanced by the European Social Fund for Sectoral Operational Programme Human Resources Development 2007-2013.

DOI: 10.1530/endoabs.37.EP1221

EP1222

Glucocorticoid resistance syndrome: case report

Ana Carolina Neves, Fernando Fonseca & Ana Agapito
Endocrinology Department, Curry Cabral Hospital – CHLC, Lisbon, Portugal.

Introduction
Glucocorticoid resistance syndrome (GRS) is a rare familial or sporadic condition, caused by mutations in glucocorticoid receptor gene. It is characterised by generalised partial resistance of target tissues to cortisol action and compensatory elevation of ACTH with subsequent hypersecretion of cortisol, mineralocorticoids and androgens. Its clinical spectrum is broad and it may occur with high blood pressure (HBP) metabolic alcalosis, hypokalaemia and virilisation.
Case report
A 19-year-old black male was referred to Endocrinology department due to HBP diagnosed at 14 years old and elevated ACTH. He had delayed psycomotor development and epilepsy since childhood. There was no history of precocious puberty. His height, weight and blood pressure were 1.70 m, 52 kg and 139/95 mmHg, respectively. No signs or symptoms of deficiency or excess of glucocorticoids, hyperandrogenism or other causes of HBP were present. Complementary exams excluded adrenal enzymatic deficiency, primary aldosteronism, phaeochromocytoma and renovascular disease as aetiology of HBP. Pituitary–adrenal axis evaluation revealed: ACTH 158 pg/ml (ND-46), cortisol(s) 08/24 h 21.9/1.8 μg/dl, cortisol (u) 102.5 μg/24 h (20–90); low-dose dexamethasone suppression test (DST): cortisol(s) 19.8 μg/dl; high-dose DST: cortisol(s) < 1.0 μg/dl. DNA analysis revealed a frameshift mutation c.2159_2160delAA, in heterozigoty in the *NR3C1* gene, not yet described in the literature. Genetic study of relatives has not been done yet, since they live abroad.
Conclusions
The clinical spectrum of GRS is broad, ranging from severe to asymptomatic forms and the biochemical profile varies, depending on the severity of the defect in the signal transduction of glucorticoids. Persistent elevated urinary cortisol and ACTH with no clinical signs of hypercortisolism in this hypertensive young man led us to suspect of GRS. Diagnosis was confirmed by the finding of a not yet described mutation of *NR3C1* gene.

DOI: 10.1530/endoabs.37.EP1222

EP1223

Bilateral adrenal haemorrhage: a rare complication of anti phospholipid syndrome

Sriranganath Akavarapu & Yee Michael
Imperial College NHS Trust, London, UK.

Introduction
Bilateral adrenal haemorrhage is a rare potentially life-threatening event that occurs either in traumatic or non traumatic conditions. We present a rare case report of bilateral adrenal haemorrhage due to anti-phospholipid antibody syndrome.
Case report
A 54 year old Iranian origin male presented with abdominal pain and collapse. His past history includes unprovoked DVT 6 months ago and off the warfarin recently. CT abdomen showed bilateral Adrenal haemorrhage. Early morning cortisol was 54. He was subsequently treated with i.v. hydrocortisone, antibiotics, fluids and made a good recovery. He had further admission within 1 week of discharge with chest pain and hypotension due to acute myocardial infarction. Coronary artery angiogram was normal. Further investigation showed positive ANA and lupus anticoagulant positive. He was discharged on oral hydrocortisone and warfarin. The diagnosis of anti phospholipid antibody syndrome was confirmed after repeat lupus anticoagulant positive at 3 months with satisfactory clinical and biochemical criteria.
Discussion and conclusion
Acute adrenal insufficiency due to bilateral adrenal haemorrhage is a rare manifestation of APS. Prompt treatment with steroids needed to achieve favourable outcome.

DOI: 10.1530/endoabs.37.EP1223

EP1224

Cushing's disease in a patient with complicated varicella

Ana Saavedra[1,2], Sandra Belo[1,2], Maria Manuel Costa[1,2], Claudia Nogueira[1,2], Paula Freitas[1,2], Ana Santos[4], Lurdes Santos[4] & Davide Carvalho[1,2]
[1]Department of Endocrinology Diabetes and Metabolism, Centro Hospitalar S. João, Porto, Portugal; [2]Faculty of Medicine, University of Porto, Porto, Portugal; [3]Instituto de Investigação e Inovação em Saúde, University of Porto, Porto, Portugal; [4]Department of Infectious Diseases, Centro Hospitalar de São João, Porto, Portugal.

Introduction
Immunossupression is a possible consequence of hypercortisolism, putting these patients in a state of increased risk of infections.
Case report
Female, 19 years old. In July 2014 she seek for medical care because she became feverish and developed an erythematous rash on her face/trunk with subsequent widespread to the entire body. She was admitted in the ICU with the diagnosis of severe varicella with acute cholestatic hepatitis and confluent necrosis of coagulative type. The patient presented full moon face (more prominent over the last 2 months), truncal obesity starting after menarche (at 10 years old), hirsutism and menstrual irregularities/secondary amenorrhea. Physical examination also showed bruises and reddish purple striae. During hospitalisation she presented hypertension, hyperglycaemia (HbA1c 6.7%) and hypokalaemia. After treatment with antiviral/antibacterial drugs and the resolution of the acute infection, she was evaluated for the suspicion of Cushing's syndrome, which was confirmed based on: high levels of serum cortisol; high 24 h urine free cortisol (300.1 μg/day); two increased late-night salivary cortisol assays (1.150 μg/dl; 0.961 μg/dl); cortisol after 1-mg overnight dexamethasone suppression test (DST) – 23.0 μg/dl; and cortisol after 2 day low-dose DST – 15.1 μg/dl. As she had high basal ACTH levels (14.7 pg/ml), it was performed a 2 day high-dose DST test (end cortisol – 3.8 μg/dl). Then it was performed a pituitary MRI, which reveals a 'lesion in the right half of the pituitary gland compatible with a microadenoma', thus confirming the diagnosis of Cushing's disease.
Discussion
This clinical case emphasizes the importance of considering hypercortisolism as a condition capable of inducing immunosuppression, which may result in the development of serious infections and, therefore, these severe clinical situations should raise this diagnostic possibility.

DOI: 10.1530/endoabs.37.EP1224

EP1225

Anaesthesia during petrosal sinus sampling and possible interference with ACTH levels

Margaret Keil, Maya Lodish, Charalampos Lyssikatos, Jaikrit Bhutani, Elena Belyavskaya & Constantine Stratakis
National Institutes of Health- NICHD, Bethesda, Maryland, USA.

Background
General anaesthesia and surgical intervention in humans are known to affect the function of the hypothalamic–pituitary–adrenal axis (HPA). In the literature there are conflicting reports about the effect of propofol, a commonly used intravenous anaesthetic agent, on HPA function.
Case reports
We report two males (11 and 12 years) with ACTH-dependent Cushing syndrome (CS) who underwent inferior petrosal sinus sampling (IPSS) with general anaesthesia. ACTH was measured from bilateral petrosal and peripheral sites at baseline and after administration of corticotrophin releasing hormone (CRH). Anaesthetic agents used included: propofol infusion (pt A: 7.8 mg/kg; pt B: 29 mg/kg), fentanyl, and midazolam. ACTH results from IPSS were atypical for both patients (i.e. no stimulation of ACTH (peripherally) and overall low values of ACTH). Since the ACTH results precluded scheduling of transsphenoidal surgery, the IPSS procedures were repeated. Results of the 2nd IPSS showed appropriate stimulation of peripheral and central ACTH levels and peripheral to central ratios consistent with Cushing disease (CD) in both patients. Anaesthetic agents used included single dose propofol at induction (~50 min prior to sampling) (pt A: 1.8 mg/kg; pt B: 1.4 mg/kg), fentanyl, and midazolam. Subsequently, both patients underwent TSS for removal of corticotropinoma which was confirmed at histology; they remain in remission of hypercortisolemia to date.
Conclusion
Historically, propofol has been shown to have direct antisteroidogenic effects on adrenal cells and to be a weak inhibitor of adrenal steroidgenesis, compared to etomidate. However, the two cases presented provide a novel insight about a possible interaction of propofol and ACTH. These cases suggest a possible short-term inhibition of ACTH secretion by propofol and highlight the importance of future research. A better understanding of the interaction of propofol with ACTH may be of vital importance in the intra- and post-operative management of patients as well as in diagnostic endocrine testing that involves anaesthesia.

DOI: 10.1530/endoabs.37.EP1225

EP1226

A case of IgG4 related hypophysitis in a Caucasian female

Anne Marie Hannon[1], Saket Gupta[1], Dave Slattery[1], Karen McGurran[1], Brendan Kinsley[2], Moshen Javadpour[3], Francesca Brett[4] & Amar Agha[1]
[1]Department of Diabetes and Endocrinology, Beaumont Hospital, Dublin, Ireland; [2]Department of Diabetes and Endocrinology, Mater Misericordiae Hospital, Dublin, Ireland; [3]Department of Neurosurgery Beaumont Hospital, Dublin, Ireland; [4]Department of Neuropathology, Beaumont Hospital, Dublin, Ireland.

IgG4 related hypophysitis is a recently described entity belonging to the IgG4 related diseases. It is characterised by markedly elevated serum IGG4 levels and tissue infiltration by IgG4 positive plasma cells. To date, 34 cases of IgG4 related hypophysitis have been described but only a handful were in women or biopsy proven. We describe a case of a 58 year old woman who presented with transient headache. She also complained of polyuria and nocturia. She had a thyroidectomy for treatment of hyperthyroidism 10 years previously. MRI pituitary revealed a pituitary mass with marked diffuse stalk thickening. Dynamic evaluation of her anterior pituitary function revealed raised prolactin and severe GH deficiency. An 8-h water deprivation test showed partial diabetes insipidus. Ferritin, serum ACE, β-HCG, alphafetoprotein, autoimmune screen and ANCA were negative. Chest and abdominal imaging and breast mammography showed no malignancy. A transsphenoidal pituitary biopsy showed evidence of hypophysitis with fibrosis and increased number of histologically benign plasma cells and >10 positive cells per HPF on IgG4 immunocytochemistry, which is highly characteristic of IGG-4 related hypophysitis. Her plasma IgG4 level was normal. She was determined to have IgG4 related hypophysitis as per the criteria proposed by Leporati *et al*. in 2011. She was commenced on glucocorticoids and is due for a follow up MRI in 6 months. IgG4 related hypophysitis is a rare disorder, which was first described in 2004 based on clinical data. Of the 34 cases recorded in the literature, 29 were men and five were women. The majority of documented cases have been from Japan. While initial case reports were of more severe disease, more recently there have been case reports of patients with milder variants, with one patient reported with normal pituitary function. Accurate diagnosis is essential, as previous reported cases have shown improvement with glucocorticoid therapy. This case illustrates that when an enlarged pituitary gland/stalk is detected, IgG4 hypophysitis should be considered in the differential diagnosis regardless of pituitary function and serum IgG4 level.

DOI: 10.1530/endoabs.37.EP1226

EP1227

Difficulties of acromegaly treatment in young patients: clinical case

Alexandru Florescu[1,2], Andra Sandru[1], Adrian Condrea[1], Liliana Moisii[1,2] & Corina Galesanu[1,2]
[1]Spitalul Sfantul Spiridon, Iasi, Romania; [2]Universitatea de Medicina si Farmacie GR. T. Popa, Iasi, Romania.

Transsphenoidal surgery still appears to be the best option for most of the patients with GH secreting adenomas. In many cases the biochemical cure targets are not reached and the patient needs adjuvant therapy. Alternatives include medical therapy with somatostatin analogues, GH-receptor antagonists and dopamine agonists. These drugs can be used alone or in combination. Radiation therapy with conventional fractionated photons or radiosurgery with proton beam could also be

effective in some cases. We present the clinical case of a 32 year old man, who first came to us in October 2008 due to acral enlargement of hands and feet, prognatism and fatigue. He had a GH level of 52 µg/l and an IGF1 level of 839 ng/ml at the time of diagnosis. After 6 months of therapy with Octreotide (Sandostatin LAR) 20 mg/28 days both of them decreased (IGF1 by 70% and GH by 80%).This treatment was maintained for 2 years, with the persistence of high levels of IGF1 (X 2009- 677 ng/ml, VIII- 767 ng/ml), but with the decrease of the tumour and the levels of GH. In august 2011 the patient underwent transsphenoidal surgery (difficult to perform due to severe bleeding and anatomical abnormalities), followed one month later by Gamma Knife. At that point he developed partial pituitary insufficiency (thyreotrop and gonadotrop), hypertension and impaired fasting glucose, for which he started medical treatment. From january 2012 he received again somatostatin analogues (the starting dose was octreotide 20 mg every 28 days for 6 months, followed by 30 mg/28 days) without the normalisation of IGF1 (X 2012-631 ng/ml, VI 2013-403 ng/ml). Because the IGF1 levels were still elevated the dose of octreotide was increased at 40 mg/28 days and GH receptor antagonists (Pegvisomant) was associated (III 2014 10 mg/day s.c.). The following IGF1 levels are still high (V 2014-493 ng/ml, VII 2014 -587 ng/ml, XII 2014-541 ng/ml). The particularity of the case is represented by the age of the patient and by the fact that throughout a relative short period of time he received the latest available therapy in acromegaly.

DOI: 10.1530/endoabs.37.EP1227

EP1228

Successful systemic treatment of Xanthoma disseminatum with cyclophospamide: an interesting case with endocrine and gastrointestinal involvement

Reyhan Ersoy[1], Sefika Burcak Polat[1], Karabekir Ercan[2], Berna Ogmen[1], Huseyin Ustun[3], Osman Ersoy[4] & Bekir Cakir[1]
[1]Endocrinology and Metabolism Department, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey; [2]Radiology Department, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey; [3]Pathology Department, Ataturk Education and Research Hospital, Ankara, Turkey; [4]Gastroenterology Department, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey.

Introduction
Xantoma disseminatum (XD) is a rare non-Langerhans cell histiocytosis (NLCH) which is often resistant to treatment. In this report, we presented a case with extensive cutaneous, hypothalamohypophysial, cerebral and gastrointestinal system involvement, which responded well to cyclophosphamide.
Case
A 16-year-old female patient admitted to our hospital with the complaints of amenorrhoea, weight gain, polidipsia, poliuria, yellow-brownish papular lesions on the cervical, periorbital, axillary and genital regions. Lesions first appeared 18 months ago and increased in amount and size in time. Hormonal evaluation was done including dynamic tests and secondary hypothyroidism, hypogonodothropic hypogonadism, GH deficiency and central diabetes insipidus were detected. Pituitary MRI demonstrated a mass 15×8 mm in diameter at hypothalamohypophysial tract together with multiple cerebral lesions. Her visual and neurologic examination was normal. A biopsy was performed on skin and duodenal lesions and the result of pathologic analysis was coherent with NLCH. In the light of those findings, she was diagnosed with XD. Hormonal replacement therapies for hypothyroidism, hypogonadism and DI were initiated. For hypothalamic mass and skin lesions 60 mg/day methyl prednisolone was started and its dosage was gradually reduced to maintenance dose of 4 mg/day. MRI screening performed at 6th month of therapy didn't show any regression in mass sizes. Hence, medical therapy was changed with cyclophosphamide 100 mg/day. No complete remission was achieved but significant regression in cutaneous, hypothalamohypophysial, cerebral and gastrointestinal lesions was obtained in 24 months. No side-effects were noticed related with cyclophosphamide. The skin lesions did not relapse after discontinuation of cyclophosphamide.
Conclusion
The coexistence of XD with hypopituitarism is a rare condition. There are various systemic treatments such as radiotherapy, cryotherapy, corticosteroids, and antiblastic chemotherapy but no single treatment is universally successful. In rare cases complete remission was obtained with low-dose oral cyclophosphamide in adults as it occurred in our case.

DOI: 10.1530/endoabs.37.EP1228

EP1229

Hyponatremia in secondary adrenal insufficiency after transsphenoidal surgery for pituitary adenoma: case report

Gordana Pemovska[1], Tatjana Bajraktarova Prosheva[2] & Sasha Jovanovska Mishevska[1]
[1]University Clinic of Endocrinology, Diabetes and Metabolic Disorders, Skopje, Macedonia; [2]Clinical Hospital, Shtip, Macedonia.

Introduction
Hyponatremia is rarely reported as a delayed complication of transsphenoidal resection of pituitary adenoma. Severe hyponatraemia can cause potentially fatal conse-quences.
Material and methods
A 34 year old patient was admitted as an urgent case at the Clinic of Endocrinology, with symptoms and signs of Addisonian crisis (dizziness, headaches, nausea, vomiting, hypotension), with muscular weakness and muscle aches, tingling hands and confusion. It was a pa-tient diagnosed with acromegaly due to STH secreting macroadenoma, with onset of symptoms 10 days after transsphenoidal pituitary surgery for macroadenoma.
Results
The biochemical analyses showed se-vere hyponatremia (Na = 116, 118, 122, 136 mmol/l). There were no hormonal dysfunctions de-tected in the pituitary–thyroid and pituitary–gonadal axis, values of STH were 1.6 ng/ml. Because of expressed slow mental process, disorientation and somnolence brain KT was made, showing reduction in the ventricular system, flattened gyri and loss of sulci suggesting cerebral oedema. The con-dition of the patient improved after the correction of hyponatremia with hydrocortisone therapy.
Conclusion
Postoperative hyponatremia after transsphenoidal surgery is more common than previously reported and may lead to fatal complications. Therefore, all patients should undergo serum electrolyte level monitoring regularly for at least 1 or 2 weeks after transsphenoidal surgery.

DOI: 10.1530/endoabs.37.EP1229

EP1230

Cushing's disease in a 7-year-boy due to corticotroph cell hyperplasia

Rosemary Dineen[1], Karen McGurren[1], Mohsen Javadpour[2], Colm Costigan[3] & Amar Agha[1]
[1]Department of Endocrinology, Beaumont Hospital, Dublin, Ireland; [2]Department of Neurosurgery, Beaumont Hospital, Dublin, Ireland; [3]Department of Paediatric Endocrinology, Our ladys hospital for Sick Children, Crumlin, Dublin, Ireland.

Introduction
Cushing's disease (CD) is very rare in children and is invariably caused by a corticotroph adenoma. However, corticotroph cell hyperplasia has only been convincingly shown in two previous cases of paediatric Cushing's disease. We report the case of a 7-year-old boy with Cushing's disease caused by coticotroph cell hyperplasia.
Case report
Our patient presented with a 10-month history of obesity, hirsutism and growth retardation. His height was 2.5S.D. below the mean and his weight was over 98th percentile for age. Examination revealed a cushingoid facies, central obesity, striae and hirsutism. Biochemical assessment showed raised 24-h urine free cortisol and mid-night salivary cortisol with failure to suppress serum cortisol following low dose dexamethasone. Baseline 0900 h ACTH level was elevated. A peripheral CRH test showed a brisk rise in ACTH and cortisol consistent with Cushing's disease. Pituitary MRI was normal. Bilateral inferior petrosal sinus sampling with CRH stimulation showed a central-peripheral gradient >3:1 at 10-min post-CRF confirming the diagnosis of pituitary dependent Cushing's. The patient underwent endoscopic transphenoidal pituitary exploration. Abnormal tissue was resected from the left side of the pituitary. Histopathology revealed no adenoma but intense immunostaining for ACTH consistent with corticotroph hyperplasia. On the fourth post-operative day, am serum cortisol level was 39 nmol/l indicating early remission. Three months post-operatively he remained hypocortisolaemic on hydrocortisone with significant clinical improvement.
Conclusion
This case illustrates that paediatric Cushing' disease may be caused, albeit very rarely, by cortricotroph hyperplasia. Careful follow-up in necessary as the recurrence rate of this entity is not known.

DOI: 10.1530/endoabs.37.EP1230

EP1231

Phaeochromocytoma patient successfully treated after seven myocardial infarctions

Krzysztof Marczewski[1,2], Iwona Ciuba[1], Andrzej Kleinrok[1,2], Tomasz Romanowicz[1] & Dorota Boniek-Poprawa[1,2]
[1]Pope John Paul II Regional Hospital, Zamosc, Poland; [2]Zamosc University of Management and Administration, Zamosc, Poland.

Introduction
Although pheochromocytoma with fatal myocardial infarction has been described over 50 years ago, diagnostics focused on catecholamine secretion is not a routine procedure post myocardial infarction.
Case report
A 49-year-old man, previously healthy, was admitted to the hospital in June 2003, with severe pulmonary oedema. Myocardial infarction was diagnosed on the basis of an increase in markers of myocardial necrosis. There was also found a significant hyperglycaemia and ketoacidosis. Coronary angiography, has not confirmed the changes in the vessels. Due to respiratory failure patient had to be mechanically ventilated. There was even a short-term cardiac arrest. After intensive treatment his status had improved and the patient left the hospital in a stable condition, require two antihypertensive drugs and insulin. In the following years (until 2012) patient has a six NSTEMI. In none of the subsequent coronary angiography important atherosclerotic lesions are visualised. The patient frequent suffered from angina and anxiety. In January 2012 in the left adrenal gland was found in the ultrasound focal lesion, confirmed in tomography as 34 mm high density lesion (50jH) with contrast retention. Hormonal diagnostics allowed diagnose adrenal pheochromocytoma. Surgery was delayed for seven and until now the last heart attack (07/05/2012). After the preparation of alpha-blocker, the patient was successfully operated on 05/09/2012. Removal of phaeochromocytoma resulted not only normalisation of blood pressure and the disappearance of the from the coronary symptoms but allowed the metabolic control and improve the patient's mental state. Currently, the patient is at a good physical and mental condition, treated with a small dose of ramipril, nebivolol and metformin.
Conclusion
The diagnosis of phaeochromocytoma is difficult, although this may change substantially fate of people affected by them. An important clue may be inadequate response to typical treatment.

DOI: 10.1530/endoabs.37.EP1231

EP1232

Primary hyperaldosteronism by Conn's syndrome: clinical case discussion

Claudia Coelho, Ana Margarida Monteiro, Vera Fernandes, Selma B Souto, Fernando Manso & Olinda Marques
Hospital de Braga, Braga, Portugal.

Introduction
Primary hyperaldosteronism (PA) is a disturbance caused by the autonomous production of aldosterone by the adrenal gland. The most frequent causes are due to bilateral supra-renal gland hyperplasia and aldesterone producing adenoma. It is most frequent amongst women aged between 30 and 50 years of age. It is clinically characterised by hypertension (HTN), resistant to therapy. Hypokalaemia, which is known as a 'classical marker' is found in less than a third of the patient and is followed by inespecific symptoms (muscle pain/weakness, polydipsy, polyuria, nocturia and parathesia). Diabetes mellitus (DM) can also be found in some cases.
Clinical case
A 55-year-old woman referred from internal medicine due to a adenoma on her right supra-renal gland with hypertension and hypokalaemia. The patient has been hypertensive for the past 16 years with the hypertension being resistant to therapy despite being on four antihypertensives (loasatran/hydrochlorothiazide 100 mg/25 mg, carvedilol 25 mg and spironolactone 50 mg). All tests were normal, except a high aldosterone/renin ratio (17.86). The patient was also diagnosed with DM and started on metformin. She was also given KCl for her hypokalaemia. A salt-loading test was carried out that confirmed the diagnosis of HP. (aldosterone 0–35.94; 4 h 56.18 ng/dl). The patient was subjected to a right sided adrenalectomy without complications leading to normokalaemia 48 h after surgery. The aldosterone/renin ratio also normalised. The patient is now able to maintain a normokalaemic state and she only needs 10 mg/day of lercanidipine to control her blood pressure.
Discussion
Due to the resistant hypertension before the age of 40 and the lack of experience with or unsatisfactory results obtained by catheterising supra-renal veins the surgical option was chosen in this case. We would like to highlight the importance of monitoring potassium levels on a weekly basis during the first month post-surgery due to the risk of transient hipoaldosteronism. With this patient we noticed an improvement in the blood pressure profile during the first month after the surgery. As described in the literature, an improvement or normalisation of hypertension can happen 1–6 months post surgery. However, due to the patient's long standing hypertension it is unlikely that this will normalise.

DOI: 10.1530/endoabs.37.EP1232

EP1233

Acute renal failure in a patient with hypopituitarism and rhabdomyolysis

Malgorzata Kaluzna, Katarzyna Piatek, Katarzyna Ziemnicka, Jerzy Sowinski & Marek Ruchala
Department of Endocrinology, Metabolic Diseases and Internal Medicine, Poznan University of Medical Science, Poznan, Poland.

Introduction
Hyponatremia can be a life-threatening emergency. Severe hyponatremia may occur in patients with hypopituitarism and secondary adrenal insufficiency and hypothyroidism. The acute decompensation of pituitary insufficiency can also lead to accompanying rhabdomyolysis and acute renal failure (ARF).
Case report
A 67-year-old woman complaining of general fatigue, dizziness, nausea, feeling cold and numbness of limbs and tongue was admitted to the emergency room. Neurological consultation was made and computer tomography (CT) showed probably old, single, hypodensic ischemic lesion of 6 mm in diameter localized subcortically in the left frontal lobe. Pale skin, loss of axillary hair and scarce pubic hair were found on inspection. The patient's past medical history was unremarkable and she had not taken drugs permanently. The patient gave birth to three, menopause occurred at the age of 52. Initial laboratory studies have shown severe hyponatremia (Na 116 mmol/l) resistant to the symptomatic treatment. Rhabdomyolysis and acute renal failure developed in the patient. Rhabdomyolysis was diagnosed on the base of elevated liver enzymes, CK-MB, CPK, and creatinine. The patient was admitted to the Department of Endocrinology. Diagnosis of complete pituitary insufficiency was made on the basis of hormonal profiles. Magnetic resonance imaging (MRI) of the pituitary has shown a very small pituitary gland. Our patient recovered after hydrocortisone and levothyroxine substitution and nephrology treatment. Due to the rhabdomyolysis and ARF the patient required appropriate hydration and a single hemodialysis treatment.
Conclusions
The diagnosis of hypopituitarism in hyponatremic patients can be overlooked and may have grave consequences. Severe hyponatremia and acute renal failure may be the leading symptoms of acute decompensation of pituitary insufficiency. Appropriate hormonal substitution with alert nephrological monitoring and management (including renal replacement therapy if necessary) are crucial in case of acute pituitary decompensation and accompanying complications treatment.

DOI: 10.1530/endoabs.37.EP1233

EP1234

Hemangiopericytoma associated hypoglycaemia and concomitant secondary adrenal insufficiency

Sinem Kiyici, Figen Topyildiz, Bunyamin Polat & Ahmet Hunuk
Department of Internal Medicine, Sevket Yilmaz Education and Research Hospital, Bursa, Turkey.

Introduction
Hemangiopericytomas (HPC) are rare vascular tumours that may be associated with hypoglycaemia. Here we report a case of HPC with multiple metastases, accompanying severe recurrent hypoglycaemia due to the combination of different aetiologies.
Case report
A 21 year-old woman was hospitalised due to loss of consciousness. The patient has been diagnosed as HPC by tibia mass biopsy 1 year ago. Tumour embolization was made several times. On admission, serum glucose was 42 mg/dl and serum insulin and C-peptide levels were suppressed. GH and cortisol response to hypoglycaemia were found insufficient. Basal ACTH was below 5 pg/ml. IGF2 was 25 ng/ml (normal range 116–358 ng/ml) and IGF2 was 823 ng/ml (normal range 288–736 ng/ml). The IGF2/IGF1 ratio was 32.9 (normal range <10), which indicates unregulated production of IGF2. Thorax and abdomen CT imaging demonstrated multiple metastatic lesions in the liver, lung, abdominal cavity, pelvis and bone. MRI revealed a microadenoma in the pituitary gland. In this case, we suggest that hypoglycaemia was associated with the combination of adrenal insufficiency secondary to deficient ACTH secretion, abnormal production of IGF2 and diminished hepatic glucose production due to the liver metastases. Because of recurrent severe hypoglycaemic attacks, a continuous glucose infusion was required to maintain normoglycaemia. Prednisolone 40 mg/day was started and a dramatically quick response was observed. Hypoglycaemic attacks were resolved immediately and 20 mg/day prednisolone was needed as maintenance therapy to prevent recurrent hypoglycaemia.
Conclusions
HPC associated hypoglycaemia is a paraneoplastic syndrome usually related with excessive production of IGF2 or partially processed forms of pro-IGF2. Hypoglycaemia can also develop by combinations of different factors such as adrenal insufficiency that we observed in the present case. The possibility of other factor must also take into consideration evaluating and treating the hypoglycaemic attacks in patients with mesenchymal tumours.

DOI: 10.1530/endoabs.37.EP1234

EP1235

An unusual case of possible cyclic Cushing's disease in a young man with Klinefelter syndrome

Thea Christoffersen[1], Anne Elisabeth Jarløv[1], Anders Juul[2], Lars Poulsgaard[3], Aase Krogh Rasmussen[1] & Ulla Feldt-Rasmussen[1]
[1]Department of Medical Endocrinology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [2]Department of Growth and Reproduction, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [3]Department of Neurosurgery, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark.

Introduction
Cyclic Cushing's syndrome (CS) is a rare disorder, characterised by alternating periods of normo – and hypercortisolism.
Case report
An 18-year-old young man was followed at the Department of Growth and Reproduction due to Klinefelter and received androgen replacement since the age of 12. As he was shifted to i.m. injections his liver enzymes increased and liver damage due to androgen replacement was suspected. A liver biopsy showed steatosis and, accordingly, androgen replacement was paused. However, the medical history revealed 20 kg weight gain, abdominal striae and mental changes, leading to evaluations for CS. Initial tests showed elevated UFC levels of 213, 238 and 397 nmol/day (ref: 12–150) and borderline abnormal 1 mg dexamethasone suppression test (DST). Over the following months, equivocal test results challenged the clinicians. Repeated long DSTs were normal, UFC levels were fluctuating and, subsequently, a peripheral CRH test showed more than 50% rise in ACTH. Finally, MRI demonstrated a 5 mm hypointense mass in the pituitary gland and an inferior petrosal sinus sampling showed a pituitary-to-peripheral ACTH-response >5, which led to the diagnosis of Cushing's disease. Two years after first CS suspicion a transsphenoidal adenomectomy was performed. Unfortunately, histology did not reveal signs of an adenoma and during the following years he presented with clinical CS features. He resumed androgen replacement to rule out androgen deficiency as responsible for the symptoms, and liver function tests were unrelated to this. Repeated DSTs showed normal suppression of cortisol despite several elevated UFCs. Thus, the cyclic manifestation of Cushing's had, very likely, relapsed. The patient had side effects to all possible registered medical therapies for Cushing's and refuses another neurosurgical procedure.
Conclusions
This case illustrates how overlapping symptoms of cyclic CS and hypogonadism due to lack of androgen replacement further hamper diagnosis and management of cyclic CS.

DOI: 10.1530/endoabs.37.EP1235

EP1236

Accelerated sarcopenia as an initial manifestation of Cushing's disease

Lakshminarayanan Pichaipillai, Mohit Kumar, Sivatharshya Pathmanathan, Denise Tiong & Claire Higham
Department of Endocrinology, Christie Hospital, Manchester, UK.

Introduction
Cushing's syndrome usually presents with a phenotype including central obesity, striae, hypertension and diabetes. We report a case of Cushing's syndrome presenting in an atypical manner.
Case
A 73 year old lady was referred to neurology with a year's history of progressive limb wasting, weakness and recurrent falls. The neurology team diagnosed accelerated sarcopenia. Investigations included CK (normal), EMG (suggested myopathic process), nerve conduction studies (no evidence of large fibre neuropathy) and muscle biopsy (atrophic change compatible with on-going neurogenic process). She had a 4-year history of hypertension and type 2 diabetes and morning cortisol was 750 nmol/l. Clinical features included progressive weight loss, immobility, severe muscle wasting and friable skin with extensive bruising and breakdown. Endocrine investigations (18 months post initial presentation) revealed: UFC 1227 nmol/24 h, midnight salivary cortisol 45.1 nmol/l, non-suppressed cortisol following LDDST at 493 nmol/l, normal potassium and ACTH 18 ng/l. Cushing's syndrome secondary to ectopic ACTH from a malignancy was considered due to the severe clinical features. Initial MRI pituitary was normal. CT whole body showed no evidence of malignancy. Dynamic pituitary MRI revealed area of reduced signal within the pituitary-likely microadenoma. A diagnosis of Cushing's disease was made and patient was started on metyrapone. On metyrapone 1 g tds her mean cortisol on day curve done by mass spectrometry was 390 nmol/l. Antihypertensives and metformin were discontinued. Concurrent intensive physiotherapy lead to the regaining of limited mobility.
Conclusion
Cushing's disease can rarely present with severe atypical clinical features that can mimic pathology of various systems, on this occasion accelerated sarcopenia, warranting neurological investigations. It is important to consider and recognise this condition early in order to prevent extreme phenotypes, where regaining full recovery may be prolonged or unattained.

DOI: 10.1530/endoabs.37.EP1236

EP1237

Grossly elevated plasma metanephrine levels due to midodrine, an α1 receptor agonist, in a patient presenting with postural orthostatic tachycardia syndrome

George Farah[1], Ashley Grossman[1], Abbi Lulsegged[2] & Nick Gall[2]
[1]Oxford University Hospitals NHS trust, Oxford, UK; [2]King's College Hospital NHS Foundation Trust, London, UK.

While phaeochromocytomas are rare tumours, their identification is essential to avoid morbidity and mortality; their biochemical identification is crucial. Plasma and 24 urinary metanephrines are used as first line investigations, with plasma metanephrines increasingly used first due to its simplicity and high sensitivity/specificity. False positive results, however, can be as high as 20%, particularly secondary to medications; their exclusion is essential to avoid unnecessary imaging and operation. However, most interfering factors cause elevation of less than fourfold above the normal range. In our case, we show the effect of midodrine- an α1 receptor agonist- in causing grossly elevated plasma, but not urinary, metanephrine. 41-year old lady was referred to our endocrine clinic in

Oxford with a possible phaeochromocytoma. She had 6-year history of dizziness and syncope, initially diagnosed with vasovagal syncope, but latterly diagnosed with postural orthostatic tachycardia syndrome (POTS). Her symptoms were episodes of dizziness, shortness of breath, nausea, headaches, with or without loss of consciousness. Her cardiovascular investigations showed sinus tachycardia and hypotension associated with her symptoms. As part of investigations, plasma metanephrines were assessed and were grossly abnormal: plasma metanephrine $>$ 25 000 pmol/l and normetanephrine of 1758 pmol/l. Her medications included midodrine 7.5 mg 3 h, bisoprolol and slow sodium. Doxazosin, an α1-adenoceptor antagonist, had recently been added following the above results. There was no relevant family history, and examination was unremarkable. Investigations included a repeat plasma metanephrines which showed similar results. However, 24-h urinary metanephrines, PTH, thyroid function and pituitary profile were normal, as was adrenal CT scan. Midodrine was then withheld for a week, and plasma metanephrines levels became normal. Doxazosin was subsequently stopped. Most reported drug interference with metanephrine levels cause mild to moderate elevation, due to a variety of mechanisms. We highlight the massive interference in plasma metanephrines assay by the α-adrenoceptor agonist midodrine.

DOI: 10.1530/endoabs.37.EP1237

EP1238

Adrenal crisis due to steroid withdrawal

Muhammad Ridhwaan Salehmohamed[1,2], Martin Cuesta[1,2] & Chris Thompson[1,2]
[1]Academic Department of Endocrinology and Diabetes Metabolism, Beaumont Hospital, Dublin, Ireland; [2]Royal College of Surgeons in Ireland, RCSI, Dublin, Ireland.

Introduction
Hen corticosteroids are utilised for their anti-inflammatory properties, adreno-cortical atrophy may result. Abrupt steroid withdrawal or intercurrent illness can precipitate acute adrenal crisis. We report two cases of adrenal crisis which resulted from withdrawal of immunosuppressive steroid therapy.
Case report
i) A 74-year-old gentleman was admitted with hypotension (BP 80/40), severe hyponatremia (Na:118 mmol/l) and acute renal failure (Creat 470 mmol/l). Despite i.v. fluids, hypotension (70/46) and renal failure (Creat 610) deteriorated; dialysis was recommended. Endocrinology consultation, for hyponatremia, elicited a drug history of prednisolone 5 mg daily for rheumatoid arthritis. The patient was treated with i.v. hydrocortisone 100 mg i.v. qds, with rapid recovery of BP (134/80), and plasma sodium (137 mmol/l). Further history revealed that prednisolone had been withheld during 48 h of bowel preparation for colonoscopy, after which the patient vomited and became delirious. The patient was unaware of 'sick day rules' and had no medicalert bracelet. ii) A 76-year-old lady was admitted for knee arthroscopy. Post operatively her plasma sodium dropped from 142 to 119 mmol/l. BP fell to 102/58 mmHg. An endocrinology consult for hyponatraemia documented that she was on prednisolone 5 mg daily for rheumatoid arthritis, but had run out of tablets 3 days prior to her admission. She had no i.v. hydrocortisone cover for anaesthesia. Random cortisol was $<$30 nmol/l. A diagnosis of adrenal crisis due to steroid withdrawal was made. She rapidly responded to i.v. hydrocortisone, and plasma sodium rose to 130 mmol/l over 36 h. The patient was unaware of 'sick day rules' and had no medicalert bracelet.
Conclusion
The case studies illustrate the vulnerability to adrenal crisis in patients on long-term immunosuppressive steroid. Patients on immunosuppressive steroids should be as aware of sick day rules as endocrine patients on adrenal replacement therapy.

DOI: 10.1530/endoabs.37.EP1238

EP1239

A cystic lesion of the adrenal gland mimicking hydatid cyst

Faten Hadj Kacem[1], Mouna Ammar[1], Ayman Maalej[2], Nesrine Cheikrouhou[1], Nadia Charfi[1] & Mohamed Abid[1]
[1]Department of Endocrinology, Sfax, Tunisia; [2]Imaging Department, Sfax, Tunisia.

Introduction
Adrenal cystic lesions are uncommon and mostly identified incidentally during radiological investigations or at surgery for unrelated reasons. Its incidence varies between 0.064 and 0.18%. Adrenal cysts are classified as endothelial cysts, pseudocysts, epithelial cysts, and parasitic cysts.
Case report
A 45-year-old female with a past medical history of systemic hypertensive disease for 2 years, presented with recurrent abdominal pain during the last 3 months. Abdominal ultrasonography (US) showed a multicystic mass in the right adrenal region. The CT scan revealed a hypo-dense, multicystic mass measuring 6$\times$5 cm in the right adrenal bed, with slightly mural enhancing after administered with contrast medium and calcifications of the cystic wall. The pictures obtained were very evocative of hydatid cyst. Hydatid serology was negative. An adrenal evaluation was performed and was within normal limits. On the basis of these findings, surgical excision was carried out. The histopathological diagnosis was a cystic lymphangioma in the right adrenal gland.
Conclusion
Cystic adrenal lymphangiomas are very rare, benign vascular lesions. Imaging can character-ize the cystic nature of these lesions. However, it sometimes fails to establish a specific diag-nosis preoperatively. So definite diagnosis relies on Histologic and immunohistochemical examination. Lymphangiomas must be kept in mind in the clinical and radiologic differential diagnosis of cystic adrenal lesions.

DOI: 10.1530/endoabs.37.EP1239

EP1240

Pituitary state during conservative treatment of prolactinomas

Anna Gusova
Scientific Research Institute of Neurosurgery n.a. N.N. Burdenko, Moscow, Russia.

Prolactinomas are the most common hormone-secreting pituitary tumors. They have good response for conservative treatment. In the time of diagnosis large pituitary tumors unrarely can cause hypopituitarism. We have two cases of partially or totally recovery of hypopituitarism in consequence of effective dopamine agonists use. The 24-years man with large prolactinoma (prolactin 52 times higher) and laboratory markers of panhypopituitarism had total recovery in 1 year of cabergoline treatment. The dramatic shrinkage of prolactinoma was observed and the last one was the secondary hypothyroidism which disappeared. The second case is 52 years old man with macroadenoma and ten times higher prolactin. He also has hypogonadism, secondary hypothyroidism and moderate hypocorticoidism (according to laboratory tests). Cabergoline, thyroxine and cortisone were administered. In 1 year despite of tumor shrinkage and prolactin normalisation, testosteron level was still undetected which was qualified as unreversible secondary hypogonadism and testosterone injection were administered. At the same time serum cortisol was at normal-low level and therapy was continued. In one more year the serum cortisol was even more high and the patient reported that he avoided to take cortisone with no consequence as for well-being. He also informed that after several testosterone injection in routine regimen the testosterone level was abnormally high so he discontinued the therapy. After laboratory tests gonadal function was found partially restored with testosterone level slightly lower than lower limit of normal, the level of cortisol was medium-high, but thyroid function remained impaired. Therefore, in case of large prolactin-secreting tumor which leads to hypopituitarism, there is still a chance of at least partially restoring of pituitary function when there is any positive size-dinamic. Our patients didn't have heavy symptoms of hypopituitarism (exept hypogonadism) and was instructed about frequence and expectance from laboratory testing. The thyroid function was the hardest to restore.

DOI: 10.1530/endoabs.37.EP1240

EP1241

Pituitary apoplexy in Cushing's disease after a standard low-dose dexamethasone suppression test

Mouna Mezoued, Djamila Meskine & Amine Habouchi
Obologhine Hospital, Algiers, Algeria.

Introduction
Pituitary apoplexy is caused by an infarction or a haemorrhage in a pituitary adenoma manifesting in acute headaches, consciousness impairment, endocrine features, and moderate to severe visual loss, with chiasmal syndrome or oculomotor palsies.

Case report
We describe here a case of a 25 years old woman, followed in our institute for a Cushing disease, and who underwent a pituitary apoplexy 24 h after a standard low-dose dexamethasone suppression test. In fact our patient presented a clinical outcome of a intra cranial hypertension, made of headache, vomiting associated to a loss of visual field and oculomotor palsies. MRI demonstrated classical signs of apoplexia. Patient was treated by cortico-therapy for one week with no response, leading to a surgical management. After what we could rapidly appreciate an improvement in the visual symptoms.
Conclusion
The clinical picture of pituitary apoplexy is characterized by the sudden onset of oculomotor palsy or blindness with acute headaches and even consciousness impairment. A functional and vital risk is present because of acute hypopituitarism. This emergency diagnosis is confirmed by tomodensitometry or magnetic resonance imaging. The association of hormone substitution and tumour transsphenoidal resection commonly leads to a positive outcome and visual improvement.

DOI: 10.1530/endoabs.37.EP1241

EP1242

Hypopituitarism after miscarriage: a case report

Ana Margarida Monteiro, Marta Alves & Olinda Marques
Department of Endocrinology, Hospital de Braga, Braga, Portugal.

Introduction
Sheehan's syndrome (SS) is a cause of partial or total hypopituitarism that occurs after postpartum pituitary infarction, in the context of serious bleeding and/or hypotension. With the advancement of obstetric care, it has become a rare disease in developed countries, but its prevalence may be underestimated. Clinical presentation is dependent on the severity of hormonal deficits, is often nonspecific and many women may be asymptomatic for years. These reasons contribute to a delay in diagnosis and in treatment of a significant cause of morbidity and mortality in affected women.
Clinical case
We report a case of a 32 years old woman sent to endocrinology consultation because of hypogonadotropic hypogonadism. Past history: menarche at 11 years with regular cycles, two pregnancies, a normal delivery without complications (17 years) and a miscarriage at 8 weeks gestation (28 years). After the miscarriage, she was hospitalised with anaemia and needed blood transfusions. She's amenorrhoeic since the miscarriage. Currently, she's asymptomatic and desires another pregnancy. On physical examination, highlight for a low BMI (17 kg/m^2). Analytically, FSH 1.08 mUI/ml (2.5–10.2), LH $<$0.07 mUI/ml (1.9–12.5), oestradiol 63.89 pmol/l (71.6–529.2), TSH 1.43 μUI/ml (0.358–3.74), FT_4 0.75 ng/dl (0.76–1.46), prolactin 4.67 ng/ml (2.8–29.2), cortisol 13.6 μg/dl (4.3–22.4), ACTH 19.7 pg/ml ($<$46), somatomedin 110 ng/ml (115–307), testosterone $<$10 ng/dl (14–76), normal DHEAS and androstenedione. Insulin induced hypoglycaemia reveals normal response of cortisol and GH. Pituitary MRI revealed a concave gland with lower dimensions than expected for her age. She was treated with levothyroxine 50 μg/day and oriented to assisted reproductive consultation.
Discussion
The patient presented corresponds to a case of hypopituitarism due to probable pituitary infarction after abortion. We emphasise the importance of the evaluation of pituitary function in women with childbirth history associated with significant blood loss, even several years after the episode.

DOI: 10.1530/endoabs.EP1242

EP1243

Acromegaly caused by atypical pituitary adenoma

Maria Manuel Costa[1,4], Ana Saavedra[1,4], Lígia Castro[2], Margarida Basto[5], Josué Pereira[3], Eduardo Vinha[1] & Davide Carvalho[1,4]
[1]Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar São João, Porto, Portugal; [2]Pathology, Centro Hospitalar São João, Porto, Portugal; [3]Neurosurgery, Centro Hospitalar São João, Porto, Portugal; [4]Faculty of Medicine, University of Porto, Porto, Portugal; [5]Neuroradiology, Centro Hospitalar São João, Porto, Portugal.

Introduction
Atypical pituitary adenomas have higher risk of aggressive behaviour in particular by the higher growth, local invasion and high risk of recurrence after surgery. In acromegaly the resistance to somatostatin analogues may be another manifestation of these adenomas since higher levels of Ki-67 are associated with poor response to therapy.
Case report
A 41-year-old woman presented to our consult with history of headaches, growth of the hands, hyperhidrosis, carpel tunnel syndrome and enlargement of the lips with 3 years of evolution. She also mentioned complaints of neck pain and reported an episode of visual changes that reversed spontaneously. Hormonal evaluation revealed the following alterations: IGF1 1687 μg/dl (64–336), GT basal 25.6 ng/ml ($<$8) and a lack of GH suppression to $<$1 ng/ml on oral glucose tolerance test. Pituitary MRI revealed pituitary lesion with 24 mm craniocaudal diameter and 5 mm transverse diameter with invasion of the cavernous sinus. She was submitted to transsphenoidal resection. Tumour pathology showed diffuse expression of GH, prolactin multifocal expression and absence of expression of other pituitary hormones. Ki-67 labelling index was 8%. Sparse representation of p53.
Conclusion
Atypical pituitary adenoma. The MRI repeated 3 months after surgery showed persistence of tissue attributable to residual tumour invading the right cavernous sinus. The patient began treatment with somatostatin analogues. This is a case of acromegaly with several predictors of a possible failure of response to somatostatin analogues: young age, elevated levels of GH and IGF1 at diagnosis, macroadenoma with invasive growth and Ki-67 labelling index of 8%. In the presence of cases of atypical adenomas a multidisciplinary team of endocrinologists, neurosurgeons, pathologists and oncologists must work together in attentive and personalised follow-up of the patient in order to prevent disease progression.

DOI: 10.1530/endoabs.37.EP1243

EP1244

Slipped upper femoral epiphysis: a rare clinical manifestation of MEN2: a case report

Laura Slattery, Jayne Doherty, Donal O'Shea, Malachi McKenna & Rachel Crowley
Department of Endocrinology, St Vincent's University Hospital, Dublin, Ireland.

Introduction
Multiple endocrine neoplasia type 2 (MEN2) comprise a group of heritable disorders that result from mutations in the RET proto-oncogene on chromosome 10. MEN2 is sub classified into MEN2A and MEN2B; these syndromes are characterised by the development of tumours at multiple sites. MEN2A is characterised by medullary thyroid cancer, phaeochromocytoma, and primary parathyroid hyperplasia.
Description/case presentation
The index case is a 49 year old female with a recent diagnosis of right phaeochromocytoma on screening for known MEN2A. Her mother had a parathyroidectomy, a partial thyroidectomy and bilateral phaeochromocytoma. The index case had a total thyroidectomy in 1980 at which time C cell hyperplasia was noted. Diagnosis was confirmed by RET oncogene mutation analysis. She has three children who are MEN2A positive and are undergoing screening. Her daughter was diagnosed with a phaeochromocytoma in 2006 with a subsequent unilateral adrenalectomy. There is also a family history of slipped upper femoral epiphysis; she had a unilateral SUFE in her teens prior to her diagnosis of MEN2A. Her daughter underwent surgery for bilateral SUFE at the age of 11 and 12. SUFE is the most common hip disorder affecting the adolescent population; there are believed to be multiple aetiological factors. In the literature, SUFE has been attributed to endocrine pathologies including hypogonadism and panhypopituitarism, deranged parathyroid hormone function and hypothyroidism. Both the index case and daughter were slim and had no history of trauma therefore atypical for SUFE.
Discussion/conclusion
We postulate that changes in parathyroid hormone or fluctuations in T_4 level in response to replacement during adolescence may have contributed to the development of SUFE in this family. Patients with MEN2A may be particularly vulnerable to this disorder because of their young age at the time of endocrine disturbance. This has not been reported previously in the literature.

DOI: 10.1530/endoabs.37.EP1244

EP1245

Simultaneous diagnosis of Graves' hyperthyroidism and adrenal insufficiency

Ifigenia Kostoglou-Athanassiou[1], Ervin Kostakis[1], Alexandros Dermentzoglou[1] & Eleni Xanthakou[2]
[1]Department of Endocrinology, Red Cross Hospital, Athens, Greece; [2]Endocrinologist, Sparti, Greece.

Introduction
Patients with autoimmune diseases are known to develop other autoimmune conditions. Adrenal insufficiency of autoimmune etiology is known to coexist with autoimmune diabetes mellitus, Hashimoto's thyroiditis and vitiligo. However, Graves' disease in the context of adrenal insufficiency of autoimmune etiology is rare.
Aim
The aim was to describe the case of a patient who presented with fatigue and was diagnosed to have hyperthyroidism and adrenal insufficiency of autoimmune aetiology.
Case report
A patient, male aged 25 years presented with fatigue, tachycardia and weight loss. He was found to have high free T_4 levels and TSH 0.001 mU/l. Antithyroid drugs were administered. However, the patient complained of continuing fatigue and weight loss. He had dark colored skin. However, when his photos were compared to older ones it appeared that his skin had a darker color. Morning cortisol and ACTH were measured. Cortisol was found to be very low and ACTH high. Cortisol was administered along with antithyroid medications and the patient improved. TSH receptor antibodies were positive and anti-adrenal antibodies were also positive. On clinical examination as well on ultrasonography the patient had no evidence of Graves' ophthalmopathy.
Conclusions
Autoimmune diseases may coexist with other autoimmune conditions, which develop usually sequentially. However, even in young patients, the simultaneous development of more than one endocrine autoimmune conditions cannot be excluded, and it should be included in the differential diagnosis, especially if symptoms persist.

DOI: 10.1530/endoabs.37.EP1245

EP1246

Fatigue as the presenting symptom of multiple endocrine neoplasia of type 2A

Nurdan Gul, Ayse Kubat-Uzum, Gulsah Yenidunya-Yalin, Refik Tanakol & Ferihan Aral
Division of Endocrinology, Department of Internal Medicine, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey.

Clinical spectrum of phaeochromocytoma syndromes are very heterogeneous. Sometimes life threatening hypertensive attacks may be the presenting symptom or the clinical picture may be subtle that a nonspecific symptom like fatigue can lead to diagnosis. We herein present two phaeochromocytoma cases with distinct clinical features.
Case 1
A 20-year-old female patient admitted to emergency department with blurred vision and headache. She experienced headache for 3 years and once she had a seizure and lost consciousness for 4 h. During the course blurred vision recurred and examination revealed papilledema and retinal haemorrhage. Thorax CT-angiography performed for a presumptive diagnosis of Takayasu's arteritis revealed a 3.5-cm right adrenal mass, and she was referred to our endocrinology clinic. She was hypertensive, and urinary catecholamines were very high. She had no family history of phaeochromocytoma and work-up for hereditary syndromes were negative. After preoperative preparation, she was successfully operated. Histopathological examination was compatible with phaeochromocytoma.
Case-2
30-year-old male patient was evaluated by his family physician because of fatigue. He was anxious as his father died of metastatic brain cancer. His laboratory evaluation revealed slightly elevated carcinoembryonic antigen. Endoscopic examination of the gastrointestinal tract was normal, but abdominal ultrasound showed 6-cm pancreatic and adrenal mass lesions, and MRI showed bilateral adrenal mass. His blood pressure was 130/90 mmHg. He did not have a history of hypertension, but he described occasional headaches. His urinary catecholamines were very high. Calcitonin level was 34.8 ng/ml. He underwent bilateral adrenalectomy, and pathologic examination confirmed phaeochromocytoma. RET protooncogen was positive, and total thyroidectomy revealed multifocal medullary thyroid cancer.
Conclusion
Even fatigue can be the presenting symptom of MEN2A, and clinical picture does not correlate with the extent of disease in phaeochromocytoma syndromes.

DOI: 10.1530/endoabs.37.EP1246

Clinical Cases - Thyroid/Other

EP1247

Ectopic ACTH syndrome due to a pancreatic neuroendocrine tumour: a case report

Juan Marti[1], Elena Zubillaga[1], Yenifer Bocangel[1] & Alfredo Yoldi[2]
[1]Hospital Zumarraga, Zumarraga, Spain; [2]HUD, Donosti, Spain.

The ectopic secretion of corticotropin from no pituitary tumours causes ~10–20% of cases of Cushing's syndrome. Enteropancreatic neuroendocrine carcinoma represents a rare cause of ectopic ACTH syndrome.
Case
A 51 years-old woman without past medical history was admitted by gain weight, facial oedema 4 months previous. Physical examination: BP 167/124, cardiac rate 49 bpm, facial oedema, troncular obesity. No others abnormalities. Laboratory test. Glucose 148 mg/dl. Kaliemia 2.8 mEq/l. Cortisol 102 µg/dl, FCU 4000 µg/24 h, chromogranin A 526 ng/ml, indolacétic acid 6.8 mg/24 h. Nocturnal cortisol 132 µg/dl, ACTH: 427 pg/ml. Nuggent test. Cortisol 129 µg/dl. Suppression with 8 mg of dexamethasone: cortisol basal 141 µg/dl, post 146 µg/dl, ACTH basal 577 pg/ml post 586 pg/ml. CT scan revealed a pancreatic mass of 30×20 mm and enlargement of adrenal glands. PET scan displayed abnormal accumulations of fluorodeoxyglucose in pancreatic area, distribution at multiple sites in the liver and enlargement of both adrenal glands. Surgical procedure was carry out, and large pancreatic tumour with multiples hepatic metastasis were observed. Pancreatectomy and splenectomy was carry out. Hystopatologycal study showed pancreatic neuroendocrine tumour, positive to cromogranin, sinaptofisine and CKAE1-AE3, Ki 67 up 50%, with lymph nodes and liver metastasis of neuroendocrine tumour. Surgical treatment of adrenal gland was discarded. Treatment with ketoconazole and metyrapone was initiated without improvement and mifepristone was added, lowering cortisol levels, however, outcome was unfavourable and patient died 3 months after diagnosis by respiratory distress and complications of Cushing's syndrome.
Discussion
Patients with pancreatic neuroendocrine carcinoma represent a rare cause of ectopic ACTH syndrome. A typical Cushingoid appearance is less frequent in ectopic ACTH syndrome. Treatment of ectopic ACTH syndrome is excision of the primary tumour. However, curative surgery is successful in only 30–47%. If the tumour cannot be resected, bilateral adrenalectomy offers effective permanent treatment. Medical cortisol inhibitors include ketoconazole, metyrapone.

DOI: 10.1530/endoabs.37.EP1247

EP1248

Bullous pemphigoid induced by vildagliptin

Bengur Taskiran[1], Bahattin Erdogan[2], Canan Solak Sisman[2] & Guven Baris Cansu[1]
[1]Yunus Emre State Hospital, Eskisehir, Turkey; [2]Eskisehir State Hospital, Eskisehir, Turkey.

Introduction
Bullous pemphigoid (BP) is an uncommon chronic, autoimmune, and subepidermal disease. It can be associated with drugs, u.v. irradiation, and X-ray therapy. There is a number of reports on bullous pemphigoid (BP) induced by DPP-IV inhibitors (vildagliptin, sitagliptin, saxagliptin). The enzyme DPP-IV degrades glucagon like peptide 1 (GLP-1), which is a potent stimulator of insulin production and secretion. DPP-IV (CD26), present as a cell surface molecule on immune cells, also plays an important costimulatory role in immune activation. We present a case of BP induced by vildagliptin.
Case report
A 59-year-old male patient who was diagnosed type 2 DM had initial HbA1c level of 12.90%. Initial therapy with premix biphasic aspart insulin bid was switched to metformin and vildagliptin 50/1000 mg combo pill bid after A1c level dropped to 5.7% at 9 months of insulin therapy, Five months after vildagliptin was started, tense vesicles 8–10 in number with an erythematous base developed over forearms and cruris. Histologic examination of lesions yielded BP. Oral antidiabetics was discontinued. He was followed up with diet alone. He did not

adhere to the therapy of oral flantadin and azathioprine and topical steroid. But the lesions regressed spontaneously after cessation of antidiabetics. Clobetasol propionate cream bid was continued. A1c was 5.7% 5 months after discontinuation of vildagliptin and metformin.

Conclusions

In the literature onset of BP lesions took 10 days to 2 years. Mostly the patients were on combo therapy with metformin. The lesions improved dramatically after cessation DPP-IV inhibitors avoiding necessity for systemic treatment for BP. Elder males predominate. This is the first case of BP induced by DPP-IV inhibitors in Turkey.

DOI: 10.1530/endoabs.37.EP1248

EP1249

Adjustment disorder and hypertensive episodes associated with cross-sex treatment with testosterone

Claudia Arnas-Leon[1], Francisco Javier Martinez-Martin[1,2], Carmen Acosta-Calero[1] & Esperanza Perdomo-Herrera[3]
[1]Hospital Doctor Negrin, Las Palmas De Gran Canaria, Spain; [2]Clinica San Roque, Las Palmas De Gran Canaria, Spain; [3]Cap Escaleritas, Las Palmas De Gran Canaria, Spain.

Introduction

Testosterone treatment in female-to-male transsexuals has been associated with worsened cardiovascular risk factors, acne, male-pattern baldness and more rarely with the onset of hypertension. Another frequent side effect of the treatment is aggression proneness -but rarely actual aggression- and increased libido.

Case report

We present the case of a 17-year old transsexual patient referred for initiation of testosterone treatment. A low initial dose (20 mg daily as a topical gel) elicited acne and mild transient mood changes (increased libido, occasional aggressive ideation) without blood pressure elevation. These symptoms improved after the first month. Three months later, after increasing the dose to 40 mg, the patient presented bouts of anger, aggression proneness, and coincidentally headache and hypertensive episodes. Secondary hypertension was ruled out and an ambulatory blood pressure monitoring showed blood pressure peaks up to 192/113 mmHg, with tachycardia up to 123 bpm and a mean activity blood pressure of 138/87 mm Hg. The patient was diagnosed of adjustment disorder, received short-course psychotherapy and testosterone was withdrawn. After one month, the mood disorder had abated, without new episodes of headache and hypertension. A second ambulatory blood pressure monitoring showed no hypertensive peaks with a mean activity blood pressure of 124/71 mmHg. According to the patient's wishes, low-dose testosterone treatment was reinstated with a scheduled slow dose progression; So far, the patient remains asymptomatic and normotensive.

Conclusions

Our patient suffered hypertensive episodes in the context of an adjustment disorder associated with testosterone treatment. Withdrawing testosterone resolved both the adjustment disorder and the hypertensive episodes. We consider that the increased blood pressure was not a direct consequence of testosterone, but an indirect result mediated by untoward psychological reactions of the patient.

DOI: 10.1530/endoabs.37.EP1249

EP1250

Submandibular ectopic thyroid with normally located thyroid gland

Mahmut Sinan Yılmaz[1], Semra Ayturk[2], Mehmet Güven[1] & Fatma Husniye Dilek[3]
[1]Department of Otolaryngology, Medical Faculty of Sakarya University, Sakarya, Turkey; [2]Department of Endocrinology and Metabolism, Trakya University Faculty of Medicine, Edirne, Turkey; [3]Department of Pathology, Medical Faculty of Sakarya University, Sakarya, Turkey.

Ectopic thyroid is a rare developmental anomaly of the thyroid gland which is defined as the presence of thyroid tissue at a site other than the pretracheal area. Nearly 1–3% of all ectopic thyroids are located in the lateral neck. Simultaneous submandibular ectopic thyroid tissue presenting with a functional orthotopic thyroid gland is extremely rare. A 37-year-old woman was admitted to our outpatient clinic with a cervical mass existing for 3 years. On physical examination, a painless, uniformly bounded, mobile, soft, nearly 3×4 cm mass was observed in the right submandibular region. A detailed systemic examination did not reveal any abnormality. Ultrasonography of the neck demonstrated a solid mass of $34\times36\times26$ mm, including cystic areas and showing significant blood flow, localized in the right submandibular region. Her thyroid gland was in a normal location and had normal parenchyma. Thyroid function tests confirmed euthyroidism and she had no anti-thyroperoxidase or antithyroglobulin antibodies. Ultrasonographyguided fine needle aspiration biopsy was non-diagnostic. Cervical magnetic resonance imaging revealed a $35\times41\times26$ mm lobulated mass showing contrast agent involvement in the right submandibular region and a normal orthotopic thyroid gland. The patient underwent excision of the submandibular mass under general anaesthesia. The histopathological examination of the mass revealed thyroid gland tissue with nodular hyperplasia. She was symptom free and euthyroid over the next year and there was no evidence of recurrence. Ectopic submandibular thyroid tissue is an extremely rare event that poses both diagnostic and management problems. However, physicians should be aware of the possibility that a submandibular mass could be ectopic thyroid tissue.

DOI: 10.1530/endoabs.37.EP1250

EP1251

Four osteopoikilosis cases detected in a family

Semra Ayturk[1], Ahmet Bilal Genç[2], Selcuk Yaylacı[2], Serdar Savas Gul[3], Ali Tamer[2] & Mehmet Celik[1]
[1]Department of Endocrinology, Faculty of Medicine, Trakya University, Edirne, Turkey; [2]Department of Internal Medicine, Sakarya University Educational and Research Hospital, Sakarya, Turkey; [3]Department of Nuclear Medicine, Sakarya University Educational and Research Hospital, Sakarya, Turkey.

Osteopoikilosis (OPK) is a rare benign sclerotic bone dysplasia. It is inherited in an autosomal dominant pattern. There is no exact evidence of its aetiology and pathogenesis. Usually, it is an asymptomatic disease and the diagnosis is made incidentally from radiographs which show multiple, small, well-defined, variably shaped and widely distributed sclerotic areas over the skeleton. We report a family with OPK. A 22 years old woman was admitted to outpatient clinic with complaints of right hip pain and fatigue for 2 years. Clinical examination was unremarkable. The patient did not have any other co-morbidity. Her laboratory and biochemical parameters were within normal limits. Numerous small round, symmetric sclerotic bone foci were detected at her pelvic radiographs. Similar lesions involving femoral head, acetabulum, sacroiliac joints, distal femur, proximal tibia as well as carpal and metacarpal bones were noted on detailed skeletal survey of the patient. Bone scintigraphy for whole body with Tc-99m was normal. Because of the radiological findings are diagnostic for OPK, family members were screened. We learned that the patient's mother and father had died. Four asymptomatic siblings were examined and three of them (two male and one female) were found to have OPK. A follow-up program was made for them. This disorder does not require any treatment and its complications are rare. However, there may be rarely associated bone tumors (such as osteosarcoma) that require follow-up. OPK is a diagnosis that should be kept in mind to avoid misdiagnosis, particularly with regard to cancer metastasis. OPK is a benign disease and invasive diagnostic procedures as well as aggressive treatment modalities should be avoided.

DOI: 10.1530/endoabs.37.EP1251

EP1252

Euthyroid Graves' ophthalmopathy in a patient with long-term amiodarone treatment

Minodora Betivoiu[1], Sorina Martin[1,2], Alexandra Nila[1] & Simona Fica[1,2]
[1]Endocrinology Department, Elias Hospital, Bucharest, Romania; [2]Endocrinology Department, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania.

Introduction

Ophthalmopathy, the most common extrathyroidal manifestation of Graves' disease, occurs in 5% of cases in the absence of hyperthyroidism. Amiodarone, an iodine-rich antiarrhythmic drug, influences thyroid function, causing thyrotoxicosis or hypothyroidism, but its effect on thyroid autoimmunity is still a matter of debate.

Case report
We report the case of a 58-year-old woman, suffering from non-sustained ventricular tachycardia, treated inconstantly with amiodarone for 27 years. Thyroid function was normal until January 2014 when she developed amiodarone induced hypothyroidism (TSH = 24 mUI/l) with negative thyroid autoantibodies anti-Tg = 0.1 UI/ml (<4), anti-TPO = 1.0 UI/ml (<20), and substitutive therapy with L-thyroxine 50 μg/day was started. Three months later the patient stopped L-thyroxine at a TSH = 0.16 mUI/l. Subsequent evaluation in August showed normal thyroid function (TSH = 3.4 mUI/l). In October she was referred to our Department for periorbital oedema, increased tearing, diplopia, mild conjunctival injection. The laboratory tests showed euthyroidism (TSH = 3.88 mUI/l), negative anti-Tg and anti-TPO antibodies, positive TRAb = 6.8 UI/l (<1). Thyroid ultrasound was normal. The eye examination revealed a clinical activity score of 4, decreased left eye motility, vertical diplopia and Hertel exophtalmometer measurements were 15 mm on the right and 17.5 mm on the left eye. The orbital CT-scan showed thickening of the left eye inferior and medial rectus muscle. The patient was treated with six pulses of intravenous methylprednisolone, 250 mg once a week, but after the third pulse she developed symptomatic bradycardia. The cardiologist recommended to stop amiodarone. The remaining pulses were well tolerated, with improvement of the eye symptoms.
Conclusion
In our case this variable thyroid status and the occurrence of euthyroid Graves' ophthalmopathy (GO) sustain the finding that in susceptible individuals amiodarone may precipitate thyroid autoimmunity due to its cytotoxic effect with a greater release of thyroid antigens. Patients with euthyroid GO need regular follow-up, because the eye involvement may develop before the appearance of clinical or laboratory signs of hyperthyroidism.

DOI: 10.1530/endoabs.37.EP1252

EP1253

Squamous cell thyroid carcinoma, the importance of early diagnosis and treatment

Isabel M Cornejo-Pareja[1], Silvia Maraver-Selfa[1], Jorge García-Alemán[1], M Victoria Ortega-Jiménez[2], Araceli Muñoz-Garach[1], Ana M Gómez-Pérez[1], María Molina-Vega[1], Cristina Díaz-Perdigones[1], Isabel Mancha-Doblas[1] & Francisco Jose Tinahones-Madueño[1]
[1]Department of Endocrinology and Nutrition, Virgen de la Victoria, Málaga, Spain; [2]Department of Pathological Anatomy, Virgen de la Victoria, Málaga, Spain.

Introduction
Squamous cell thyroid carcinoma is a very rare malignant epithelial tumour. It presents as rapid growth cervical mass, may affect neighbour structures and sometimes metastasizes other parts of the body. It's often associated with previous goiter history and occasionally with autoimmune thyroiditis. It can appear pure, as a component of undifferentiated carcinoma, or combined with differentiated carcinoma areas (papillary or follicular).
Case report
A 31 years old woman, with goiter family history (mother and paternal aunt). Without any previous history or cervical radiotherapy. She presented an anterocervical lump, without compressive discomfort. Physical examination: multinodular goitre (MNG) grade 2. Neck ultrasound: bilateral MNG with endothoracic projection and left prevalence with 3 cn dominant nodule. Biochemistry: TSH 1 μUI/ml. Ultrasound-guided FNA: colloid nodule with cyst formation. X-ray chest: left-extrinsic tracheal mark. Because of nodule size and endothoracic projection, we decided total thyroidectomy. Histopathology: colloid nodules with peripheral areas of squamous metaplasia, including nuclear atypia area, mitosis and p53 expression suggestive of squamous carcinoma transformation, the tumour doesn't exceed the capsule, there were no lymphatic or vascular infiltration. Extension post-surgery, we apply for a thyroid ultrasound with suggestive image of scar tissue in left thyroid bed and PET-CT was negative. Oncology Service examined our case, no adjuvant treatment was recommended. Currently, three years after surgery, the patient remains free of disease.
Conclusion
Squamous cell thyroid carcinoma is an aggressive tumour, usually lethal. It requires rapid diagnosis. The best option of treatment is radical surgery, only possible if early diagnosis, as in our case. The use of postoperative external radiotherapy or adjuvant chemotherapy should be considered because of the high rate of local recurrence of these tumours.

DOI: 10.1530/endoabs.37.EP1253

EP1254

A rare case of triple parathyroid adenoma with hyperparathyroidism occurring at a young age

G Gonca Oruk[1], Mehmet Haciyanli[2], Melike Bedel Koruyucu[3], Ebru Rüksen[4], Ozlem Gur[2], Cengiz Tavusbay[2], Husnu Yilmaz[1] & Baris Pamuk[1]
[1]Division of Endocrinology and Metabolism, Ataturk Training and Research Hospital, Izmir Katip Celebi University, Izmir, Turkey; [2]Department of Surgery, Ataturk Training and Research Hospital, Izmir Katip Celebi University, Izmir, Turkey; [3]Ataturk Training and Research Hospital, Ankara Yildirim Beyazit University, Ankara, Turkey; [4]Deparment of Nuclear Medicine, Ataturk Training and Research Hospital, Izmir Katip Celebi University, Izmir, Turkey.

Lesions causing primary hyperparathyroidism (PHP) can be summarised as solitary adenoma (80–85%), multiglandular hyperplasia (15%), parathyroid carcinoma (1%). While double adenomas are identified in 2–15% of the patients which are operated for PHP, triple adenomas are very rare. The case is presented because in the recent years patients who are admitted to the hospital with intense bone complaints are very unusual and multiple adenomas are also seldom. 22 years old female patient was admitted to orthopaedics outpatient clinic with symptoms of severe pain with activity and mass at proximal area of left femur. During evaluation calcium and parathyroid hormone (PTH) levels were discovered to be high. Calcium: 11.8 mg/dl, phosphorus: 2.2 mg/dl, alkaline phosphotase (ALP): 1275 U/l, PTH: 2754 pg/ml, 24 h urine calcium: 288 mg/day, BUN: 5 mg/dl, creatinine: 0.41 mg/dl, 25 (OH) D Vitamin: 3.2 μg/l. Thyroid doppler ultrasonography revealed a 20×17×7 mm mass at the right lobe of the thyroid and at the caudal region of this lesion a 13×11×9 mm mass, also a 36×22×23 mm lesion at the left lobe of the thyroid continuing to the mediastinum consistent with right and left-sided parathyroid adenomas. 20 mCi Tc-99m MIBI SPECT images demonstrated hyperdense activity only at the left side. Before the operation the patient was screened for multiple endocrine neoplasia because of her young age, results were negative. After the operation three parathyroid adenomas were discovered and PTH and calcium levels regressed to 10 pg/ml and 8.4 mg/dl respectively. Usually PHP is expected to occur at later stages of life, but PHP should also be kept in mind in patients with serious bone complaints, high calcium and PTH levels. Early diagnosis and appropriate treatment can be prevent morbidity and mortality related with PHP.

DOI: 10.1530/endoabs.37.EP1254

EP1255

A case of Gitelman syndrome with normomagnesemia: do detailed history and basic laboratory tests provide correct diagnosis?

Yumi Harano, Yurika Akiyama, Kazufumi Honda & Hiroko Arioka
St Luke's Medical Center, Tokyo, Japan.

Introduction
Gitelman syndrome (GS) is autosomal recessive disorder, characterised by hypokalemia, hypomagnesemia, metabolic alkalosis and low urinary calcium excretion. We report a case with final diagnosis of GS using the DNA analysis, presented with severe hypokalemia but normomagnesemia.
Case report
A 47-year-old Japanese male presented to our hospital because of severe hypokalemia in the annual health check-up. Severe hypokalemia was pointed out in the previous check-up, but he was reluctant to be investigated. He was totally asymptomatic and had no history of muscle weakness, palpitation and syncope. He denied the use of any medication including laxative and diuretics. He was normotensive and no growth retardation. The laboratory test revealed that the serum potassium was 1.7 mEq/l but he had no hypomagnesemia. His 24 h-urinary calcium excretion, 75 mg/day, was not so impaired. We analysed his genetic mutation by direct DNA sequencing. As a result, he had two genetic mutations on SLC12A3 which encoded the thiazide-sensitive NaCl cotransporter. These genetic mutations are found in the majority of GS patients. We established a final diagnosis of GS based on his history and genetic mutations.
Discussion and conclusion
To make a diagnosis of GS, many aetiologies should be excluded. Especially, Bartter syndrome is an important genetic disorder to distinguish. Especially, type III Bartter syndrome has similar features with GS, adult-onset, no growth retardation, preserved renal function and similar electrolyte abnormalities. To evaluate serum magnesium and urinary calcium excretion were important for the differential diagnosis. In this case, the serum magnesium was normal and urinary calcium excretion was not decreased. This case didn't have classical features

of GS. To identify the genetic mutation is very important to establish a diagnosis of GS. When the laboratory findings are not typical for GS, direct DNA sequencing can be useful test to distinguish with Bartter syndrome.

DOI: 10.1530/endoabs.37.EP1255

EP1256

Clinical features and surgical approach of thyroid pathology in patients over 65 years

Mihai Radu Diaconescu[1], Ioan Costea[1], Mihai Glod[1], Mirela Grigorovici[1] & Smaranda Diaconescu[2]
[1]IVth Surgical Clinic. 'Gr T Popa' University of Medicine and Pharmacy, Iasi, Romania; [2]Vth Pediatric Clinic 'Gr T Popa' University of Medicine And Pharmacy, Iasi, Romania.

Introduction
The significant increase in the average lifespan of the general population lead to a proportional enhancement in the prevalence of benign and malignant thyroid conditions and equally the number of surgeries for this pathology.
Patients and method
In a personal series of 464 thyroid disorders undergoing surgery over two decades we recorded 51 patients (21.5%) aged over 65 years of which 11 (2.4%) having over 75 years. Demographic, clinical and diagnostic characteristics of these cases were together with indications, management practice and outcome.
Results
There have been recorded 33 females and 18 males ($R=1/1$) with clinically, laboratory and histologically confirmed diagnosis in which were 22 (multi) nodular goitres (47%) among 16 six plunging goitres some with compressive phenomena, 18 (35.2%) – two Basedow diseases, nine multinodular toxic goitres and seven toxic adenomas and also nine thyroid carcinomas (17.6%) of which six were differentiated and three anaplastic tumours. Thirty-four total or near-total thyroidectomies of which three with cervical lymphadectomy and 17 conservative exercises were performed. There were not postoperative deaths but we recorded two cases each of prolonged hypocalcaemias, recurrent laryngeal nerve paresis and one recurrence. In all benign cases we obtained a stable in time cure while in obtained in four papillary tumours.
Discussions
Our series as well as literature data emphasises out of increased prevalence of thyroid geriatric disorders underling peculiarities related of sometimes delayed occurrence and prolonged evolution, atypical or imprecise symptomatology with less conclusive bioassays, coexistence of burdensome comorbidity all of them with direct consequences of a possible surgical sanction. In terms of clinical and lesional aspects outside thyroid nodules and especially micro-nodules that can accommodate any substrate, hyperthyroidism are more often (multi)nodular and they have mostly atypical manifestations, ophthalmopathy and hyperkinetic syndrome being sometimes replaced by an 'apathetic' presentation with weight loss and predominantly cardiovascular syndrome j arrhythmia and cardiac failure. Finally thyroid carcinomas have increased aggressiveness, accelerated evolution, higher incidence of anaplastic forms. Principles of thyroid surgery in the elderly are the same with those adopted at younger ages also taking into account the pathological load of the subjects and its mandatory preoperative correction.
Conclusions
Despite some difficulties in diagnostic and additional risks related to comorbidity benign and malignant pathology installed in patients over 65 years, may benefit of all types of conservative or radical thyroidectomies in terms of strict monitoring individualised in each case.

DOI: 10.1530/endoabs.37.EP1256

EP1257

Incidental papilar carcinoma and large goitre in extremely obese patient with excessive daytime sleepiness

Milina Tancic-Gajic[1], Svetlana Vujovic[1], Miodrag Vukcevic[2], Miomira Ivovic[1], Ljiljana Marina[1], Zorana Arizanovic[1] & Dragan Micic[1]
[1]Faculty of Medicine, Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia, University of Belgrade, Belgrade, Serbia; [2]Faculty of Medicine, University Clinical Hospital Center Bezanijska Kosa, University of Belgrade, Belgrade, Serbia.

Introduction
In adults, the most common cause of obstructive sleep apnoea is obesity. Other causes are anatomical craniofacial bony abnormalities, neurologic syndromes, alcohol and sedatives use, hypothyroidism, acromegaly and rarely thyroid goitre. Untreated obstructive sleep apnoea can lead to serious complications, including cardiovascular diseases, accidents, and premature death.
Case report
A 56-year-old patient was referred to a pulmologist due to excessive daytime sleepiness. Patient has primary hypothyroidism adequately treated with a constant daily dose of levothyroxine (L-T_4). The scores for the Epworth sleepiness scale was 18. The severe obstructive sleep apnoea (OSA) was confirmed by polisomnography (Respironics Alice 5): apnoea-hypopnea index (AHI) was 32.6/h. Spirometry showed a restrictive pattern related to obesity. Due to primary hypothyroidism and obesity examination by an endocrinologist was advised. Patient was extremely obese - BMI 45.3 kg/m^2 with neck of 50 cm in circumference and large goitre. Ultrasonography of the neck revealed a large goitre with significant retrosternal propagation and some thyroid nodules. Volume of the right lobe was 120 ml, whereas the volume of the left one was 92 ml with a tracheal compression. Due to large goitre a total thyroidectomy was conducted. Pathohistology report was showed chronic lymphocytic thyroiditis and papilar carcinoma with diameter of 1.8 cm in the left lobe. The patient postoperatively received therapeutic dose (3.7 GBq) of ^{131}I. There were no significant changes of the patient's weight. Six months after the surgery polysomnography was repeated. A mild form of OSA (AHI 12.3/h) was present.
Conclusion
Thyroid cancer coincided with large goitre which was an additional cause together with extreme obesity for OSA. In obese patients with excessive daytime sleepiness, additional endocrine causes of OSA should be considered.

DOI: 10.1530/endoabs.37.EP1257

EP1258

A rare cause of syndrome of inappropriate antidiuretic hormone

Mutlu Niyazoglu[1], Esra Hatipoglu[2], Burcugul Kaya[1] & Sadi Gundogdu[3]
[1]Division of Endocrinology, Department of Internal Medicine, Istanbul Research Hospital, Istanbul, Turkey;
[2]Division of Endocrinology, Department of Internal Medicine, Edirne Government Hospital, Edirne, Turkey; [3]Division of Endocrinology and Metabolism, Department of Internal Medicine, Cerrahpasa Medical School, University of Istanbul, Istanbul, Turkey.

Introduction
Acute intermittent porphyria (AIP) is an autosomal dominant disorder resulting from partial deficiency of the haeme biosynthetic enzyme porphobilinogen deaminase.
Case report
A 17-year-old female presented with progressive abdominal pain. She had history of recurrent abdominal pain and darkening in urine colour. She was on lansoprazol and metaclopramide, initiated 2 days earlier. She did not have additional personal or relevant family history. Physical examination did not reveal any pathologic finding.
Laboratory findings were as following: glucose: 84 mg/dl (N: 74–106), urea: 14 mg/dl (N: 17–43), creatinin: 0.6 mg/dl (N: 0.5–0.9), sodium: 103 mmol/l (N: 136–146), potasium: 3.6 mmol/l (N: 3.55.1), chloride: 76 mmol/l (N:101109), ALT: 21 U/l (N: 035), CK: 281 U/l (N: 0145), triglyceride: 46 mg/dl (N: 0–150), total protein: 6.9 g/dl (N: 6.6–8.3). In urine sediment erythrocyte was 11 p/Hpf (N: 0–2), leucocyte was 60 p/Hpf (N: 0–2), and nitrite was (+). Search for euvolemic hyponatraemia was initiated. Sodium in spot urine was 95 mmol/l, urine osmolarity was 490 mOsm/kg and plasma osmolarity was 230 mOsm/kg. TSH was 3.1 IU/ml (N: 0.3–5.6) and basal morning cortisol level was 34 μg/dl (N: 6.7–22.6). She was diagnosed with syndrome of inappropriate ADH. Plasma Na level was gradually increased up to 133 mmol/l with infusion of %0.3 NaCl solution. Chest X ray, cranial MRI and abdominal ultrasonography did not reveal any abnormality. Based on her history of periodic abdominal pain and dark urine porphyria was suspected. Porphoblinogen in 24-h urine sample was 19.7 mg/24 h (N: 0–1.6) and total porphyrin was 646 μg/24 h (N: 0–100). She did not have any cutaneous lesions. With the laboratory findings and her personal history she was diagnosed with inappropriate ADH syndrome secondary to AIP. The acute attack of AIP was taken under control with glucose loading and antibiotherapy for urinary tract infection.
Conclusion
It is important not only to treat syndrome of inappropriate ADH, but also to address any underlying condition. Diagnosis and management of AIP can be challenging and close monitoring for complications is needed.

DOI: 10.1530/endoabs.37.EP1258

EP1259

Fine needle aspiration biopsy: a method to distinguish between thyroid nodules and parathyroid adenomas

Alina-Andreea Gatu[1,2], Cristian Velicescu[1,2], Stefana Bilha[1,2], Voichita Mogos[1,2] & Dumitru Branisteanu[1,2]
[1]University Hospital 'Sf. Spiridon', Iasi, Romania; [2]University of Medicine and Pharmacy 'Grigore T. Popa', Iasi, Romania.

Introduction
High-resolution ultrasound (US) allows the location of large parathyroid adenomas. These tumours should be however differentiated from thyroid nodules. For the confirmation of the parathyroid adenoma, we propose US-guided fine-needle aspiration biopsy (FNAB) of suspected nodules, with additional parathyroid hormone (PTH) analysis in the washout of the aspirate (PTH-FNA).
Case report
A 51-year old woman with recently installed menopause and a history of kidney lithiasis and fragility fractures attended our hospital for the investigation of a multinodular goitre. The measurement of bone mineral density assessed by dual X ray absorptiometry showed that the patient was severely osteoporotic, with lowest score on distal 1/3rd of the radius. Despite the presence of complications, the high PTH level (281 pg/ml) was accompanied by only marginally increased serum calcium (10.1 mg/dl). This discrepancy may be explained by the co-existence of D hypovitaminosis (11 ng/ml). Ultrasound investigation revealed the presence of a multinodular goitre containing five nodules, one of them showing features suggestive for a large parathyroid adenoma. We measured high PTH levels only in the FNAB washout from the suspected parathyroid adenoma, but not in that extracted from the largest of the other thyroid nodules. The patient was submitted to total thyroidectomy due to compressive complaints and excision of the parathyroid adenoma. Immediately after surgical intervention, the PTH levels normalised. Histology confirmed pre-surgical localization of the parathyroid adenoma and revealed that one of the thyroid nodules contained an *in situ* papillary carcinoma.
Conclusion
PTH-FNA is a reliable and possibly a more accurate and faster method than additional imaging techniques to localise a large parathyroid adenoma in patients with concomitant thyroid nodules.
Disclosure
This work was supported by the European Social Found, Human Resources Development Operational Programme 2007-2013 'DocMed.net_2.0' is POSDRU 159/1.5/S/136893.

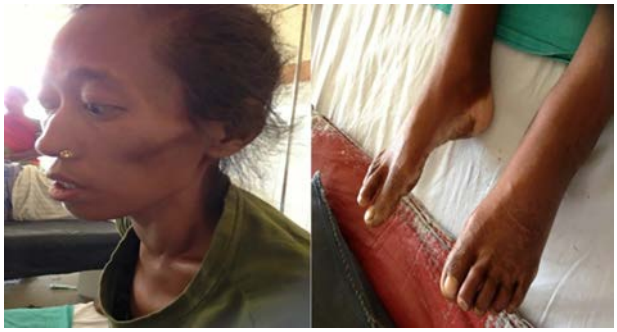
DOI: 10.1530/endoabs.37.EP1259

EP1260

Hypercoagulable state: an evidence of linkage with hyperthyroidism

Kunjang Sherpa, Robin Maskey, Prahlad Karki, Deebya Raj Mishra, Denish Peeyush & Naveen Pandey
B.P. Koirala Institute of Health Sciences, Dharan, Nepal.

Introduction
Hyperthyroidism is not a widely recognised association with Venous thromboembolism (VTE). However, Several previous studies suggest that hyperthyroidism represent a potential hypercoagulable and hypofibrinolytic state, which may contribute to the increased risk of thromboembolism.
Case report
A 39-year-old lady presented with Swelling over bilateral lower limbs for 1 month, Palpitation for 1 month. She had history of swelling over neck for last 13 years and protrusion of bilateral eye for 13 years, history of increased sweating, anxiety, and weight loss of about 10 kg in last 6 months. On examination patient had staring appearance, atrial fibrillation, She also had pallor, bilateral exophthalmos ('NO SPECS'-2), Diffuse goiter bilateral and non pitting pedal edema with hyperpigmented plaques over dorsum of leg and foot. Investigation revealed thyroid function test- TSH = <0.05 mIU/l, $fT_3 = 29.8$ pmol/l, $fT_4 = >100$ pmol/l and anaemia (haemoglobin of 9 mg/dl). Venous Doppler ultrasound (USG) revealed presence of an echogenic thrombus in bilateral lower limb extending into femoral vein in right side and up to popliteal vein in left side and USG neck showed diffusely enlarged thyroid gland with heterogenous echotexture with increased vascularity. The patient was treated with antithyroid drugs,anticoagulants, and β-blockers. The patient improved clinically with normalization of thyroid function.



Taken with permission

Conclusion
Our case report reinforces the available evidence on the possible role of overt hyperthyroidism as VTE risk factor. It seems worthwhile to measure thyroid hormones in patients with unprovoked venous thromboembolic event and in contrarily the diagnosis of venous thromboembolism should be considered in patients with hyperthyroidism, particularly if additional prothrombotic risk factors are present.

DOI: 10.1530/endoabs.37.EP1260

EP1261

Atypical subacute thyroiditis

Guzin Fidan Yaylali[1], Zeynep Dundar Ok[2], Mehmet Sercan Erturk[1], Fulya Akin[1] & Senay Topsakal[1]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Pamukkale University, Denizli, Turkey; [2]Department of Internal Medicine, Faculty of Medicine, Pamukkale University, Denizli, Turkey.

Introduction
A diagnosis of subacute thyroiditis (SAT) is readily suspected when patients present with a particular set of typical clinical and laboratory characteristics. We present a patient with atypical SAT who had no neck pain but presented with fever, and weight loss; had thyrotoxicosis with normal 99mTc uptake, and needed higher doses of steroids to resolve.
Case report
A 57-year-old man presented with a fever (39 °C) of 2 month-duration. Physical examination was unremarkable. Laboratory analysis revealed WBC: 10 550 K/ul, hemoglobin: 10 g/dl, erythrocyte sedimentation rate: 102 mm/h, C-reactive protein: 17 (<0.5) and normal renal, hepatic function tests. Hepatitis and human immunodeficiency virus serologies were negative. Toxoplasmosis, Epstein-Barr virus, and cytomegalovirus IgM and IgG titers were negative. Blood and urine cultures were also negative. Serum protein electrophoresis showed no abnormality compatible with multiple myeloma. Computed tomography of the neck, thorax and abdomen showed jugular, mediastinal, parailiac and retroperitoneal lymph nodes in nonpathological size. Biopsy of a lymph node showed lymphoid hyperplasia. Transthoracic echocardiography did not show any finding compatible with infective endocarditis. TSH: 0.412 IU/ml (0.2–4.2), fT_3: 14 pg/ml (2.8–4.3), fT_4: 0.9 ng/dl (1.04–1.65), anti-TPO: 16 (0–34), anti-TG: 32 IU/ml (0–115), TSH receptor antibody: 0.4 U/l (<1.8), thyroglobulin: 14 ng/ml (0.83–68). Thyroid ultrasonography did not show any nodules. Thyroid scintigraphy showed normo-active, diffuse hyperplastic thyroid gland. Methimazole and propranolol were initiated. But his fever did not resolve until 60 mg of methylprednisolone was given with the diagnosis of SAT. After steroid treatment, fT_3 levels decreased which had increased previously with methimazol.
Conclusion
This case presented atypically in that he had no neck pain but was diagnosed with SAT while being worked up for the fever of unknown origin. Interestingly, he had normo-active thyroid gland and his fT_3 levels increased to very high levels in disproportion to his fT_4 levels. Higher doses of steroids were needed to resolve his fever and normalize his fT_3 levels. This report illustrates that the diagnosis and treatment of SAT can sometimes be difficult.

DOI: 10.1530/endoabs.37.EP1261

EP1262

New treatments of diabetes: a promising alternative to bariatric surgery in obese patients

M Mar Roca-Rodríguez, Isabel Mancha-Doblas, M José Picón-César, Ana María Gómez-Pérez, Isabel Cornejo-Pareja, María Molina-Vega, Cristina Díaz-Perdigones, Gabriel Olveira-Fuster & Francisco J Tinahones
Department of Endocrinology, Virgen de la Victoria and Regional Hospitals, Malaga, Spain.

Introduction
New treatments of diabetes improve global metabolic status beyond glycemic control and achieve weight reduction in many patients.
Case reports
We described four case reports to show GLP-1 agonists and dapaglifozin effects on metabolism and weight in patients with type 2 diabetes and obesity.
Case 1 (Liraglutide)
A 48-year-old man, hypertension, type 2 diabetes and extreme obesity. Baseline visit: treatment enalapril 20, acetylsalicylic acid 100, metformin 850. Weight 191 kg, BMI 60.9 and HbA1c 6.6%. After 4 months under treatment with liraglutide: weight 158 kg, BMI 50.4 and HbA1c 5.3%.
Case 2 (Exenatide lar)
A 58-year-old man, type 2 diabetes and extreme obesity. Baseline visit: weight 141 kg, BMI 50 and HbA1c 6.7%. After 4 months under treatment with metformin 850 and exenatide lar: weight 133 kg, BMI 47 and HbA1c 6%. After 10 months under treatment with metformin 850 and exenatide lar: weight 127 kg, BMI 44.9 and HbA1c 5.5%.
Case 3 (Lixisenatide)
A 52-year-old woman, hypertension, type 2 diabetes and extreme obesity. Baseline visit: treatment metformin 850, simvastatin 20, losartan 100, atenolol 50. Weight 138 kg, BMI 55.4 and HbA1c 9%. After 4 months under treatment with metformin 850 and lixisenatide: weight 133 kg, BMI 47 and HbA1c 6%. After 10 months under treatment with metformin 850 and lixisenatide: weight 125 kg, BMI 48.8 and HbA1c 5.7%.
Case 4 (Dapaglifozin)
A 64-year-old man, type 2 diabetes, dyslipidaemia and grade 1 obesity. Baseline visit: treatment metformin 850 and simvastatin 40. Weight 106 kg, BMI 34.2 and HbA1c 8.8%. After 5 months under treatment with dapaglifozin: weight 93.6 kg, BMI 31.8 and HbA1c 6.6%.
Conclusion
GLP-1 agonists and dapaglifozin got ssignificant improvement of anthropometric parameters and glycaemic control in patients with type 2 diabetes and obesity. They were safety and well tolerated, and could represent a promising alternative to bariatric surgery.

DOI: 10.1530/endoabs.37.EP1262

EP1263

Graves' disease in a mediastinal mass presenting after total thyroidectomy for nontoxic multinodular goitre

Filipe Cunha[1,2], Elisabete Rodrigues[1,2], Joana Oliveira[1,2], Luís Vinhas[3] & Davide Carvalho[1,2]
[1]Serviço Endocrinologia, Diabetes e Metabolismo do Centro Hospitalar São João, Porto, Portugal; [2]Faculdade de Medicina da Universidade do Porto, Porto, Portugal; [3]Serviço de Cirurgia Geral do Centro Hospitalar São João, Porto, Portugal.

Introduction
Thyrotoxicosis after total thyroidectomy (TT) is mostly iatrogenic. Rarely, an hyperfunctional thyroid remnant or ectopic tissue may be the cause. We report a case of Graves's disease in a mediastinal thyroid mass presenting 7 years after TT for nontoxic goitre.
Case report
A 67-year-old woman presented with palpitations, fatigue and weight loss. She had a history of TT for nontoxic multinodular goitre at the age of 60 without any signs of malignancy on microscopic examination. She was medicated with levothyroxine 100 μg/day since the surgery without follow-up. She was tachycardic and had no cervical mass nor eye involvement. The TSH levels were suppressed (0.000 μU/ml) and the free T_4 (3.22 ng/dl) and free T_3 (8.46 pg/ml) increased. No mediastinal enlargement nor trachea deviation on chest roentgenogram. Levothyroxine treatment was stopped but patient showed no improvement on free T_4 or free T_3 10 days later. Thyroglobulin was increased: 294 mg/ml. Cervical ultrasound revealed no thyroid remnant. Anti-TSH receptor antibodies were high (19.7 U/l). Corporal scintigraphy demonstrated increased intrathoracic radioiodine uptake. CT scan confirmed a 60×40 mm mediastinal mass. Methimazole 10 mg/day was started. Three months later her thyroid function was normal and she was submitted to surgical resection. Microscopic examination showed thyroid tissue with no signs of malignancy.
Conclusions
Although thyrotoxicosis after TT is mostly due to excessive supplementation, true hyperthyroidism may be the cause. The presence of thyroid tissue after TT in our patient may correspond to a remnant or an ectopic thyroid tissue that became hyperfunctional in the presence of anti-TSH receptor antibodies.

DOI: 10.1530/endoabs.37.EP1263

EP1264

Severe hyponatremia in the course of autoimmune polyglandular syndrome type 2 of atypical clinical picture

Maria Kurowska, Joanna Malicka, Jerzy & Stanisław Tarach
Department of Endocrinology, Medical University, Lublin, Poland.

Introduction
Severe hyponatremia defined as the blood sodium concentration below 115 mmol/l is rarely recognised in the course of autoimmune polyglandular syndrome type 2 (APS t.2). The aim of the paper is to present the female patient with severe hyponatremia preceding the diagnosis of APS t.2 of atypical clinical picture.
Case report
A 54-year-old woman with the diagnosis of psoriasis established 10 years earlier and treated for psoriatic arthritis from 7 years. She was admitted to the emergency ward because of persistent vomiting, hyponatremia = 111 mmol/l and hyperkaliemia = 5.4 mmol/l. For several months she observed increasing fatigue, hypotension, recurrent abdominal pain, loose stools, increased appetite for salt, progressive darkening of the skin and weight loss of 12 kg/6 months. Her ACTH level was 857.3 pg/ml; blood cortisol in the morning was: 3.7; 1.6 μg/dl and in the evening: 2.7, 1.7 μg/dl. Lack of adrenal response after stimulation with Synacthen and normal adrenal CT image were confirmed. 21-hydroxylase autoantibodies were negative (1: <10). FT_4-32.2 pmol/l; FT_3-16.2 pmol/l; TSH <0.004 mIU/l. Antibodies antiTPO-4659 U/ml; antiTG-391 U/ml, TRAb-1.8 U/ml. USG revealed 12 ml thyroid gland with numerous, hypoechogenic, small (4 mm) areas in both lobes. The diagnosis of primary adrenal insufficiency with concomitant autoimmune thyroid disease with hyperthyroidism in a patient with psoriatic arthritis was established. Summary. Psoriatic arthritis and thyroid disease with thyrotoxicosis are rare components of APS type 2 and hyponatremia occurs more frequently in patients with concomitant hypothyroidism.
Conclusion
Severe hyponatremia in our patient could be the result of a significant increase in demand for cortisol caused by thyrotoxicosis and the lack of opportunity to increase its production by the adrenal cortex.

DOI: 10.1530/endoabs.37.EP1264

EP1265

Diabetes mellitus in a patient with Leri–Weill dyschondrosteosis

Didem Ozdemir[1], Sefika Burcak Polat[1], Nagihan Bestepe[1], Saliha Ozbek[2], Reyhan Ersoy[1] & Bekir Cakir[1]
[1]Department of Endocrinology and Metabolism, School of Medicine, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey; [2]Department of Internal Medicine, Endocrinology and Metabolism, School of Medicine, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey.

Introduction
Leri–Weill dyschondrosteosis (LWD) is a rare autosomal dominant dyschondrosteosis characterised by Madelung deformity and mesomelic dwarfism. Majority of cases are associated with haploinsufficiency of the short-stature homeobox-containing (SHOX) gene. Here we report a patient with LWD and diabetes mellitus (DM).
Case report
A 31 years old man applied with polyuria and polydipsia. He did not have any chronic disease. In family history, father had type 1 and mother had type 2 DM. His height was 146 cm and weight was 62 kg, with a BMI of 29.1 kg/m^2.

Laboratory investigation revealed a fasting blood glucose of 298 mg/dl, HbA1c 13.4%, insulin 8 μU/ml (2.6–24.9), C-peptide 1.65 ng/ml (0.1–3.6). AntiGAD, anti-insulin and islet-cell antibodies were negative. Intensive insulin treatment was started. The result of genetic analysis made to determine cause of short stature about 1.5 years ago was 45,X,-Y[5]/46,X,der(Y)t(Y;Y)(p11.2;q11.21). There was deletion in the SHOX gene of Y chromosome. He had bilateral Madelung deformity which is an epiphyseal growth plate disturbance characterized by shortened and bowed radii and ulnae leading to dorsal dislocation of the distal ulna. Thus, he was diagnosed to have LWD.
Conclusion
Haploinsufficiency of the SHOX gene which is located on the pseudoautosomal region of both the X- and Y-chromosomes is a cause of short stature in various clinical conditions including LWD. There are previous reports indicating inverse association between height and diabetes, and showing increased prevalance of gestational DM in patients with short stature. In the literature, clinical features of LWD is limited to skeletal anomalies and short stature. This is the first report of DM in a patient with this syndrome. Although, it is probable that this might be just a coincidence, we think possible association between impaired glucose metabolism and syndromes related with short stature needs further investigation.

DOI: 10.1530/endoabs.37.EP1265

EP1266

Hyponatraemic encephalopathy induced by single dose of indapamide

Naik Haya & Karim Noordally
Eastbourne Hospital, East Sussex, UK.

Introduction
Hyponatraemia is the most common of electrolyte abnormalities. There are numerous factors which may directly cause or contribute to hyponatraemia, including dehydration, concomitant cardiac/hepatic/renal disease, and certain medications, such as diuretics. Hyponatraemia may cause a range of symptoms, depending on the speed and severity of the deficiency. Mild hyponatraemia (>115 mmol/l), can causes malaise, nausea and vomiting. Significant hyponatraemia, $[Na^+]<115$ mmol/l, manifests with confusion, seizures, and ultimately coma. Chronic, 'asymptomatic' hyponatraemia has been shown to cause gait disturbances, falls and neurocognitive impairment.
Case
A 76-year-old lady was brought into A&E, having been found collapsed at home. GCS was 6/15.She was confused and agitated. She was euvolaemic, and had normal blood glucose. CT-head showed no acute intracranial abnormality. Laboratory work up showed a profound hyponatraemia, Na^+108. Prior to this admission, her sodium levels were within normal ranges. Full-body CT scan, which showed no neoplastic cause for her hyponatrameia. Her past medical history also included asthma, IHD, and primary hypothyroidism. She was smoker, although she denied any new respiratory symptoms, or weight loss. She reported having commenced indapamide for hypertension one day prior to presentation.
Laboratory work
$K+4.2$ mmol/l; corrected calcium 2.13 mmol/l, TSH 9.9 mU/l, FT_4 18 pmol/l. Her urinary osmolality was 475 mOsm/kg; urinary $[Na^+]$ was 27; serum osmolality, 236, serum cortisol was 761 nmol/l. Indapamide was stopped and she was put onto fluid restriction, with a strict input/output chart. She had regular $[Na^+]$ checks, which showed gradual improvement in the hyponatraemia: 108 mmol/l on day 0, 111 mmol/l on D1, 120 mmol/l on D2, 127 mmol/l on D3. She was notably less confused and agitated on discharge, and, when reviewed in clinic a 4 weeks later, her symptoms had resolved entirely. More recent biochemistry shows normal sodium.
Conclusion
Diuretics are associated with hyponatraemia. However this is the first reported case of hyponatraemia and encephalopathy after single dose of indapamide.

DOI: 10.1530/endoabs.37.EP1266

EP1267

Noninfectious but genetic bilateral neck swelling

Capraro Joel, Nagel Wolfgang, Clerici Thomas, Stöckli Sandro, Brändle Michael & Bilz Stefan
Kantonsspital St.Gallen, St.Gallen, Switzerland.

Introduction
We describe a case of a 32 year old woman with bilateral carotid body tumours as initial finding of a paraganglioma syndrome type 1.
Case
A 32-year old previously healthy mother was referred because of bilateral neck swelling, presumably lymphadenopathy, associated with recurrent upper respiratory tract infections during the past year. Cervical ultrasound raised the suspicion for bilateral carotid body tumours which were confirmed by MR-imaging and a subsequent DOPA-PET-CT, which showed no evidence for multifocality or metastases. Plasma metanephrines including methoxytyramine were within the normal range and although a family history was negative, the genetic work-up revealed a SDHD mutation (paraganglioma syndrome typ 1). Because of mass effects and the patients wish, resection of the right sided tumour has been scheduled.
Discussion:
HNPGLs are rare tumours (incidence 1:30 000 – 100 000) derived from extraadrenal chromaffin cells and 95% arise from the parasympathic nervous system, typically the carotid body (glomus caroticum), jugular bulb (glomus jugulare) and different branches of the vagal nerve (glomus vagale, glomus typanicum). Plasma methoxytyramine may be elevated (1/3 of cases), normally they are clinically nonsecretory and present because of their mass effects. Around 35% are associated with a genetic defect, with SDHD-mutations accounting for $>50\%$, SDHB for 20–35% and SDHC for 15% (extraordinary SDHAF2). The inheritance pattern is autosomal dominant for SDHx mutations, but in SDHD and SDHAF2 maternal imprinting is postulated. Malignancy is rare (3.5%) although metastases occur up to 20 years after initial diagnosis. Staging is performed by functional imaging with ^{18}F-DOPA- or ^{68}Ga-DOTATATE-PET-CT, anatomical imaging with CT and/or MRI gives a better locoregional resolution. Surgical resection may be associated with significant morbidity especially caudal cranial nerve injury. Radionuclid-therapy or radiotherapy/-surgery must be evaluated as alternatives. Genetic counselling and testing is mandatory due to the high rate of germline mutations and familial disease.

DOI: 10.1530/endoabs.37.EP1267

EP1268

Hypercalcaemia; a silent indolent course?

Ruth Casey, Larissa Higgins, Aoife Lowery, Michael Kerin & Conal Dennedy
Galway University Hospital, Galway, Ireland.

A 83-year-old lady presented to hospital with a one week history of malaise, dyspnoea and chest pain. Her admission bloods revealed a markedly elevated calcium of 4.16 mmol/l. Further investigations revealed a PTH of >5000 ng/l. Clinically the patient had poor dentition which had developed over the past 3 years and a history of episodic abdominal pain and constipation. For investigation of primary hyperparathyroidism, she had an ultrasound neck, which revealed an enlarged 8 cm left parathyroid gland. She was initially managed with intravenous bisphosphonate, i.v. fluids and i.v. furosemide, once intravascularly volume replete. As part of her initial workup, she underwent a CT pulmonary angiogram. This revealed acute subsegmental pulmonary emboli, a cystic pancreatic lesion, sequelae of previous pancreatitis, nephrolithiasis and possible medullary sponge kidney. Swift surgical referral was sought because of concern of possible parathyroid carcinoma. Once her calcium was optimised and the patient was medically fit, a minimally invasive parathyroidectomy was carried out. Surgical dissection included a sliver of the left thyroid lobe to ensure clear surgical margins with the aforementioned suspicion of a parathyroid carcinoma. The high risk of hungry bones was anticipated and the patient was given vitamin D by intramuscular injection pre operatively and a bed was booked in the high dependency unit post operatively to facilitate an arterial line and frequent close monitoring of ioinsed calcium levels. Fortunately the patient only required four intravenous infusions of calcium. Within five days of her surgery the patient was discharged. The histology revealed a parathyroid adenoma with no suspicious or mitotic features. This case acts a reminder that although primary hyperparathyroidism is often considered a benign entity, life-threatening hypercalcaemia can develop and requires urgent management. It highlights the multi-systemic sequelae that can occur with chronic hypercalcemia and reminds us that parathyroid carcinoma although rare, must always be considered when markedly elevated levels of parathyroid hormone and hypercalcaemia are encountered.

DOI: 10.1530/endoabs.37.EP1268

EP1269

The association between Graves' disease and thyroid cancer: coincidence or causality? Case report

Stefana Bilha[1,2], Ionut Repede[3], Alina Gatu[1,2], Radu Danila[4], Cristian Velicescu[4], Voichita Mogos[1,2] & Dumitru D Branisteanu[1,2]
[1]Endocrinology Clinic, 'Sf. Spiridon' Clinical Emergency Hospital, Iasi, Romania; [2]Department of Endocrinology, University of Medicine and Pharmacy 'Gr. T. Popa', Iasi, Romania; [3]Department of Endocrinology, 'Sf. Pantelimon' Hospital, Focsani, Romania; [4]Surgery Clinic III, 'Sf. Spiridon' Clinical Emergency Hospital, Iasi, Romania.

Introduction
Graves' disease (GD) has been related to a higher incidence of thyroid cancer. Thyroid nodules found in GD seem to have a higher risk for malignancy. The prognosis of thyroid cancer may be aggravated by the association with GD.
Case report
We present the case of N.I, a 56-year-old woman diagnosed with multinodular goitre and overt hyperthyroidism for which therapy with carbimazole 40 mg/day was started. She was referred to our Endocrinology Department 2 months later for follow-up. She complained of important weight loss, palpitations, fatigability and recent swelling of the neck. Clinical examination revealed a painless large goitre and mild exophthalmia. Laboratory findings still showed subclinical hyperthyroidism (TSH = 0.013 μUI/ml – normal range 0.4–4 and FT_4 = 0.957 ng/dl – normal range 0.89–1.76). TSH antibodies (TSAb) were present in high titres and GD diagnosis was established. Thyroid ultrasound revealed a large conglomerate mass with microcalcifications in the left lobe on the background of a hypoechoic, hypervascular goitre. FNAB from the nodule revealed cytology highly suspicious of malignancy. Total thyroidectomy was performed and histopathology report showed invasive papillary thyroid carcinoma follicular variant and typical findings of GD. After surgery, the patient underwent radioactive iodine (^{131}I) therapy. The post-therapy whole-body radioiodine scan showed remnant thyroid tissue and multiple iodine-avid lung metastases. Thyroglobulin levels remained abnormally elevated, making the patient a candidate for an additional radioactive iodine administration.
Conclusions
This is a rare case of simultaneously diagnosed GD and thyroid carcinoma. The tumour had a rather invasive and aggressive phenotype, in contrast to histopathology and in accordance with studies proposing GD as a negative prognostic factor in thyroid cancer. We suggest managing patients with thyroid cancer and GD according to high-risk protocols. We recommend a closer ultrasound follow-up for nodules in GD and the performance of FNAB when nodules are found.

DOI: 10.1530/endoabs.37.EP1269

EP1270

Severe hypocalcaemia and hypomagnesaemia secondary to omeprazole

Claire Min-Li Teo, Timothy Peng Lim Quek & Shaikh A K K Abdul Shakoor
Tan Tock Seng Hospital, Singapore, Singapore.

Introduction
Proton pump inhibitors (PPIs) are commonly prescribed drugs. We report a case of severe hypocalcaemia secondary to omeprazole-induced hypomagnesaemia.
Case report
A 85-year-old Chinese man with stage 4 chronic kidney disease was admitted to our hospital in Jun 2014 with vomiting and weakness. On admission, he was severely hypocalcaemic (adjusted calcium 1.37 mmol/l (RI: 2.15–2.58)) and hypomagnesaemic (Mg 0.1 mmol/l (RI: 0.7–1.0)). Serum phosphate and 25-OH vitamin D levels were normal. Intact PTH done after normalisation of serum magnesium showed secondary hyperparathyroidism (intact PTH 61.0 pmol/l (RI: 0.8–6.8)). An inpatient endocrinology referral was made for persistent hypocalcaemia. Review of his medical records revealed initiation of omeprazole in 2010 for peptic ulcer prophylaxis when he was prescribed short course prednisolone for gout. Omeprazole was continued after prednisolone cessation. Severe hypomagnesaemia and hypocalcaemia was also noted during two previous admissions to another hospital in Nov 2013 and Jun 2014. Calcium levels were normal between hospitalisations but magnesium levels were not rechecked.
In view of the possibility of omeprazole induced hypomagnesaemia and hypocalcaemia, omeprazole was stopped and changed to famotidine. With electrolyte replacement and a short course of calcitriol, serum calcium normalised within 4 days and remained normal at follow-up with calcium carbonate 1.25 g bd (as a phosphate binder) and no magnesium supplementation.
Conclusion
Severe hypomagnesaemia with hypocalcaemia is a rare side effect of PPI use. PPI use may alter intestinal absorption of magnesium, resulting in hypomagnesaemia, which then in turn impairs PTH secretion and action, causing hypocalcaemia. Correction of magnesium levels by stopping the PPI and aggressive magnesium replacement is hence essential before correction of the hypocalcaemia can be achieved. It is therefore important to have a high index of suspicion for this potentially life threatening side effect in patients on omeprazole presenting with hypocalcaemia.

DOI: 10.1530/endoabs.37.EP1270

EP1271

Late-diagnosed primary hyperparathyroidism resulting in loss of kidney and advanced osteoporosis

Malgorzata Jacewicz, Anna Zielinska, Anna Poplawska-Kita, Malgorzata Szelachowska & Maria Gorska
Department of Endocrinology, Diabetology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland.

Introduction
The report describes the case of a late-diagnosed primary hyperparathyroidism in the patient, who developed catastrophic renal complications and such advanced osteoporosis, that hungry bone syndrome occurred after removal of parathyroid adenoma.
Case report
A 63-year-old woman with long-lasting nephrolithiasis was admitted to the hospital due to high PTH discovered in a routine laboratory testing. She had undergone left-side nephrectomy 2 years before admission due to hydronephrosis. In the last year she lost 5 kg and suffered from asthenia, joint-pain and recurrent infections of the urinary tract. Laboratory tests during hospitalisation confirmed significantly raised PTH (2070 pg/ml), ALP (1047 IU/l), total calcium, and ionized serum calcium (3.26 and 1.91 mmol/l respectively). Also, anaemia (Hb, 8.8 g%) was observed and serum creatinine was substantially deteriorated (2.12 mg/dl, GFR 19 ml/min). Calcium (92.4 mg) and phosphate (367 mg) urine excretion in 24 h collection and 25(OH)D3 (17 ng/ml) were under normal range. Neck ultrasonography demonstrated multinodular goitre (thyroid function tests were normal). The biggest nodule was in the right thyroid lobe, it was hypoechogenic and had 20×16×24 mm diameter. 99mTc-sestamibi scintigraphy detected abnormal lower right parathyroid gland. DXA osteodensitometry showed advanced osteoporosis (−4.8 S.D. lumbar and −3.6 S.D. femoral neck *T*-score). During the parathyreoidectomy rapid decrease of serum PTH was observed (to 150 pg/ml). Two months postoperatively patient developed hypocalcaemia (1.93 mmol/l) and again high level of PTH (946 pg/ml). The diagnosis of hungry bone syndrome was made. The treatment with vitamin D, calcium supplementation, and alendronate sodium was started, which resulted in a gradual decrease in PTH and normalization of serum calcium.
Conclusion
In each case of nephrolithiasis the probability of hyperparathyroidism should be checked, otherwise it can lead to irreparable damages of human organism.

DOI: 10.1530/endoabs.37.EP1271

EP1272

Acute thyroiditis due to nocardia associated to thyrotoxicosis

Isabel Torres-Barea[1], Rosa Márquez-Pardo[1], Gloria Baena-Nieto[1], Francisco J Vilchez-López[2], Manuel Cayón-Blanco[1], Lourdes García-García-Doncel[1] & Rosario López-Velasco[1]
[1]Hospital de Jerez, Jerez de la Frontera, Spain; [2]Hospital Puerta del Mar, Cádiz, Spain.

Introduction
Acute thyroiditis is an uncommon illness that exceptionally presents with thyrotoxicosis. Differential diagnosis mainly includes subacute thyroiditis. Nocardia asteroides is an opportunistic pathogen, with the majority of infections occurring in immunocompromised patients, as the delay in diagnosis due to negative blood cultures makes it potentially letal.

Case report
We present a case of acute thyroiditis due to Nocardia that presents with thyrotoxicosis in a patient with diabetic nephropathy that received a kidney cadaveric transplantation. A 44-year-old woman with diabetic nephropathy had a cadaveric renal transplant. About 3 months later, she presented neck pain accompanied by fever, dysphagia, enlargement of thyroid gland and thyrotoxicosis. These findings together with image tests were consistent with subacute thyroiditis. However, worsening of symptoms despite usual treatment and the finding of an abscess in the ultrasonography study made us formulate the possibility of an acute thyroiditis. Fine-needle aspiration of the abscess and drainage were performed and Nocardia asteroides was isolated in the fluid culture. Owing to abscess persistence despite of drainage and specific antibiotic therapy surgical thyroidectomy was made.
Conclusions
Acute thyroiditis due to Nocardia is exceptional, with only six published cases in the literature, none of them presenting with thyrotoxicosis. It is the second known case of Nocardia thyroiditis in a patient with solid transplant organ, being the rest in patients under corticosteroids treatment. Nocardiosis is typically regarded as an opportunistic infection occurring in immunocompromised hosts and is it to be taken into account in these patients.

DOI: 10.1530/endoabs.37.EP1272

EP1273

Adrenal embolisation in severe ectopic Cushing: unusual case and extraordinary measures

Ismene Bilbao, Luisa Antuñano, Izaskun Olaizola, Ana Chacon, Estela Elias, Nerea Egaña, Cristina Garcia, Maite Aranburu, Alfredo Yoldi & Miguel Goena
Hospital Universitario Donostia, San Sebastian, Spain.

Introduction
Pancreatic ACTHomas have a poor prognosis with severe and rapidly progressive clinical courses, influenced by hypercortisolaemia thus whenever possible, control of the cortisol levels should be obtained to reduce complications. We report the use of adrenal embolisation in a case of a life threatening paraneoplastic Cushing.
Case
A 51-year-old woman with a negative past medical history complained of general weakness. Cushing's syndrome was suspected on the basis of hypokaliaemia, new onset hyperglucaemia and metabolic alkalosis found in the laboratory tests run on admission. She had no Cushingoid features except mild plethora. The suspicion was confirmed by high levels of urinary free cortisol, serum cortisol and ACTH, a lack of circadian rhythm of serum cortisol, and a low (1 mg) and high dose (8 mg) overnight of dexamethasone tests that failed to suppress. CT and whole body PET scan showed 2×3 cm mass in the pancreas tail. She underwent the excision of the pancreatic mass and pathology confirmed the neuroendocrine nature of the tumour. Cushingoid features were more obvious and liver metastases were observed so treatment with ketokonazol was started, initially decreasing cortisol levels, but refractory hypercortisolemia recurred although dose was increased and metopirone added. The patient became psychotic so mifepristone was commenced, but she continued to deteriorate. It was therefore decided that an attempt should be made for bilateral adrenalectomy, but the patient was unfit for surgery so a bilateral adrenal embolectomy was performed. A week after the procedure her condition improved and the urinary cortisol levels lowered. Unfortunately the patient died soon after due to a multiorganic failure.
Conclusions
Aggressive attitudes to control cortisol levels are necessary to reduce comorbidities in ectopic Cushing. This case shows that adrenal embolectomy might be of some use when the patient has become unfit for surgery and in whom medical therapy has failed.

DOI: 10.1530/endoabs.37.EP1273

EP1274

Primary hyperparathyroidism in pregnancy

Hanna Komorowska, Barbara Brominska, Maciej Biczysko, Bartosz Luftmann, Wojciech Pienkowski & Marek Ruchala
University of Medical Sciences in Poznan, Poznan, Poland.

Introduction
Hyperparathyroidism during pregnancy is a serious problem. Appropriate management is a matter of debate. We would like to present cases in which, PHP was diagnosed in completely different circumstances, though end up with various pregnancy outcomes.
Case report
First patient was 29-year-old women in 21th week of her second pregnancy admitted to our ward due to suspected relapse of Graves' disease and possible adrenal dysfunction. She presented with weakness, abdominal pains, vertigo in 7th week of pregnancy. During hospitalisation, previous suspicions were ruled out. Unexpectedly, we discovered elevated concentration of total calcium. After thorough examination, we confirmed a diagnosis of hyperparathyroidism. Owing to biochemical deterioration she was operated in 24th gestation week. The women gave birth to a healthy baby girl in 40th week of gestation. Second patient was 28-year-old women admitted to Outpatient Endocrinology Clinic due to hypercalcaemia. Medical history revealed miscarriage in 9th week. During pregnancy which she lost, calcium levels were very high. On the day of visit neck ultrasonography depicted a hypoechoic region which could be consistent with enlarged parathyroid gland. She was operated. Frozen section pathology and intraoperative PTH assay confirmed diagnosis of parathyroid adenoma and curative procedure.
Conclusion
Presented cases highlight the importance of controlling calcium-phosphate balance in pregnancy. Decisions concerning method of treatment PHP are difficult. When conservative procedures are introduced, mother and her child should remain under strict control. On the other hand operation during pregnancy is hazardous. Our experience gives a novel insight into that complicated problem. Taking into account possible adverse effect of PHP on health of both women and fetus there are growing evidence pro surgery, regardless of gestational age.

DOI: 10.1530/endoabs.37.EP1274

EP1275

Thyroid tuberculosis mimicking carcinoma: case report

Samir Ait Abderrahmane, Yamina Aribi, Zoubir Sellal, Merieme Bensalah, Leila Brakni, Samia Ouldkabli & Zahra Kemali
Central Hospital of Army, Algiers, Algeria.

Tuberculosis of the thyroid gland occurs rarely, and should be considered in the diagnosis of nodular lesion of the thyroid gland. We report the case of a 44-year-old woman admitted for therapeutic management of a suspected goiter appeared at 2 months of hospitalisation and quickly increasing in volume in a few days, she had a goiter clinically type 2, firm, homogeneous, without palpable nodules in it, hardly moving with swallowing movements with slight dysphagia without signs of thyroid dysfunction. Cervical ultrasound: found a suspicious mass in the right thyroid lodge. FNA of cervical mass found the CPE side for a very granulomatous thyroiditis DeQuervain IDR A Tuberculin had regained energy. The patient received a total thyroidectomy before the signs of malignancy on ultrasound. Histology was in favor of a histopathology of thyroid and thyroid localization soft tissue died a Caseo folliculaire.mise tuberculosis TB treatment with good clinical course.
Conclusions
Thyroid tuberculosis is a rare disease, which can take various forms, especially you must think in TB endemic area, the diagnosis is histological and/or bacteriological. Treatment is primarily medical, based on a combination of anti tuberculosis. Preoperative diagnosis of thyroid tuberculosis is important because of the availability of medical treatments and the limited role of surgery.

DOI: 10.1530/endoabs.37.EP1275

EP1276

Case report: superior vena cava syndrome secondary to intrathoracic goitre

Bruno Francisco García-Bray[2,3], Nieves Cruz Felipe-Pérez[1], Ricardo Darias-Garzón[1], Benigno Rivero-Melián[1] & Ignacio Llorente-Gomez de Segura[1]
[1]Hospital Universitario Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Spain; [2]Orden Hospitalaria San Juan de Dios, Santa Cruz de Tenerife, Spain; [3]Hospital Quirón, Santa Cruz de Tenerife, Spain.

Introduction
We introduce a case involving the appearance of superior vena cava syndrome secondary to intrathoracic goitre. We discuss the diagnosis, prognosis and treatment applied to this pathology.
Case report
A 67-year-old woman who presents respiratory distress, cough, and weight loss. After physical examination and a chest radiography showing a mass that occupied the upper and middle right lung lobes, a neoplasm is suspected and at first, palliative radiotherapy is indicated. Chest and abdomen CT are done before treatment and an intrathoracic goitre is diagnosed. Following this finding, surgical treatment is performed.
Conclusions
When a superior vena cava syndrome is diagnosed, additional tests should be performed to discover the real aetiology of the syndrome, which in this case corresponds to a giant intrathoracic goitre. Thyroid function tests and imaging techniques such as ultrasound or CT are indicated in these cases. The treatment of choice of the intrathoracic goitre is surgical removal, especially in cases where compression of adjacent structures is present.

DOI: 10.1530/endoabs.37.EP1276

EP1277

Clinical and hormonal characteristics of a series of patients affected by inappropriate TSH syndrome: insights into the differential diagnosis

Sefika Burcak Polat, Cevdet Aydin, Mina Gulfem Kaya, Neslihan Cuhaci, Reyhan Ersoy & Bekir Cakir
Endocrinology and Metabolism Department, Ataturk Education and Research Hospital, Yildirim Beyazit University, Ankara, Turkey.

Introduction
Normal or elevated TSH level in the presence of elevated T_4 is defined as 'inappropriate TSH syndrome'. Two main clinical conditions that can lead that syndrome are TSH-secreting adenoma (TSHoma) and resistance to thyroid hormone (RTH). Making the correct diagnosis is crucial in order to decide the most appropriate treatment option. Herein we presented clinical and laboratory data of seven patients who were hospitalised for the differential diagnosis of the two clinical entities.
Method
Our database was reviewed for the patients diagnosed with inappropriate TSH syndrome at our hospital between 2010 and 2014. After exclusion of the other rare causes of inappropriate TSH syndrome, seven patients who were hospitalised for the differential diagnosis of TSHoma and RTH were included in this report.
Result
Age of the patients was changing between 20 and 52 years. Clinically two patients were asymptomatic, three had tachycardia and weight loss and one had goitre. Final diagnosis was RTH in four patients, TSHoma in two and unequivocal in one. Two patients diagnosed with TSHoma were operated and had positive staining with TSH. Both of the TSHoma cases had macroadenoma on pituitary MRI and visual field defect while two of four patients with RTH had microadenoma. Alpha-subunit/TSH molar ratio was above 1 in all patients diagnosed with TSHoma while it exceeded 1 in two patients with the final diagnosis of RTH. TRH stimulation test revealed a blunted response in all patients with TSHoma and a positive response (increase $>100\%$) was observed in all with THR. TSH was suppressed after T_3 suppression test in all patients with the final diagnosis of RTH.
Conclusion
Differential diagnosis of RTH and TSHoma can be a clinical challenge and requires complex hormonal tests and imaging methods. Since incidental pituitary tumours are not rare, presence of an adenoma should not rule out diagnosis of RTH.

DOI: 10.1530/endoabs.37.EP1277

EP1278

Autoimmune polyglandular syndrome: case report series

Raluca Nan[1], Cristian Guja[1,2], Andra Caragheorgheopol[1,3], Dana Manda[3], Gabriela Radulian[1,2] & Madalina Musat[1,3]
[1]University of Medicine and Pharmacy 'Carol Davila', Bucharest, Romania; [2]National Institute of Diabetes, Nutrition and Metabolic Disease 'Prof. Dr. N. Paulescu', Bucharest, Romania; [3]National Institute of Endocrinology 'C.I. Parhon', Bucharest, Romania.

Introduction
The polyglandular autoimmune syndromes (PAS) are rare conditions characterised by the failure of several endocrine glands sometimes associated with other non-endocrine autoimmune diseases. There are four categories of PAS: PAS-I includes at least two out of: mucocutaneous candidiasis, hypoparathyroidism and adrenocortical failure. PAS-II comprises of Addison's disease, autoimmune thyroid disease and/or type 1 diabetes (Carpenter's syndrome). PAS-III is defined by the presence of other autoimmune disorders than Addison's disease and hypoparathyroidism, while PAS IV includes non-endocrine autoimmune disorders and Addison's disease, but not hypothyroidism.
Case reports
We present three cases of a larger series of PAS type II/III. The first case is of a 55-year-old woman, who was diagnosed with PAS-II (Addison's disease, autoimmune thyroiditis and latent autoimmune diabetes in adults). The second case is of a 42-old man, so far diagnosed with Basedow's disease, type 1 diabetes and vitiligo. The third case is of a 22-year-old woman, diagnosed with type 1 diabetes mellitus and primary hypothyroidism so far. The occurrence of autoimmune diseases can continue in the latter two cases, therefore PAS-III could evolve into PAS II.
Conclusion
We emphasise the importance of screening for PAS after the first autoimmune disease is diagnosed. The key to successfully managing patients with PAS is to identify and treat their disorders early before complications occur. This may be achieved by early screening for autoantibodies or subclinical endocrine failure. Patients should be educated to comply with the lifelong medical surveillance and encourage their family members to be screened for autoimmune diseases as about 50% of patients with PAI II have siblings with autoimmune diseases.
Disclosure
This work was supported by the 'CERO – PROFIL DE CARIERA: CERCETATOR ROMAN', contract no POSDRU/159/1.5/S/135760, project co-financed by the European Social Fund through Sectoral Operational Programme Human Resources Development 2007–2013.

DOI: 10.1530/endoabs.37.EP1278

EP1279

Similia similibus curentur: a novel treatment approach in endocrinology?

Regina Streuli[1,2], Lea Slahor[2], Lukas Burget[2], Christoph Henzen[2] & Stefan Fischli[2]
[1]Division of Endocrinology, Diabetes, Osteology and Metabolism, Departement of Medicine, Kantonsspital, 9007 St. Gallen, Switzerland; [2]Division of Endocrinology, Diabetes and Clinical Nutrition, Departement of Medicine, Luzerner Kantonsspital, 6000 Luzern 16, Switzerland.

Introduction
Hyperinsulinaemic hypoglycemia after gastric bypass surgery is a rare but probably underestimated complication. The mechanisms leading to hypoglycemia are complex and incompletely understood and involve several factors: A part from decreasing insulin resistance, caloric restriction and alteration of nutrient delivery, enhanced secretion of insulin and incretins (GLP1 and GIP), altered physiology of other hormones and dysregulation of counterregulatory effectors seem to play a major role. Treatment strategies include nutritional counselling with carbohydrate restriction and various medical treatments. Partial pancreatectomy is reserved for severe treatment-refractory cases.
Case report
A 53-year-old woman presented with postprandial hypoglycemia and neuroglycopenia 3 years after Roux-en-Y gastric bypass. A CGMS over 1 week demonstrated several hypoglycemic episodes typically occurring 2–3 h after meals. Endogenous hyperinsulinism was documented in a mixed meal test which was stopped after 2 h when the patient had severe neuroglycopenic symptoms and a plasma glucose of 1.9 mmol/l. ^{18}F-DOPA-PET showed diffuse uptake within the pancreas but no focal enhancement. Despite carbohydrate restriction the patient continued to have neuroglycopenic symptoms. Diazoxide was begun but had to be withdrawn due to side effects. After discussion of other treatment options, the patient was started on liraglutide (Victoza) which was titrated to a dose of 1.2 mg daily. Frequency and severity of postprandial hyperinsulinemic hypoglycemia decreased markedly and neuroglycopenia resolved completely.
Conclusions
GLP1 analogues might be a new treatment option for hyperinsulinaemic hypoglycemia after bariatric surgery. However, the exact mechanism of action remains to be elucidated. It can be assumed that a stimulation of glucagon secretion with concurrent inhibition of insulin secretion in low blood glucose

states by GLP1 analogues partly explains the stabilising effect on glucose metabolism in these patients. Nevertheless, further studies are needed.

DOI: 10.1530/endoabs.37.EP1279

EP1280

The use of omega-3 free fatty and medium chain triglycerides in combination with GLP1 and SGLT2 in the management of obesity and severe refractory hypertriglyceridaemia

Yusniza Yusoff[1], Yong Sy Liang[1], Foo Geong Taat[1] & Khoo Kah Lin[2]
[1]Hospital Tengku Ampuan Rahimah, Klang, Selangor, Malaysia; [2]Pantai Medical Center, Kuala Lumpur, Malaysia.

Hypertriglyceridaemia and obesity are common encounter in diabetic patients. It is often refractory to conventional treatment especially those with a very high triglyceride (TG) levels. The institution of medium chain diet (MCT) and fish oil in addition to the liraglutide and SGLT2 and conventional insulin has rendered significant and a satisfactory triglyceride, and glucose level as well as weight reduction. We would like to illustrate a case of 35 years old lady with a different treatment modality apart from the current general approach in managing obesity and hypertriglyceridaemia. There was marked reduction in HbA1c, 12.1–9.2% within 2 months. This is accompanied with weight reduction of 6 kg within four months. While the triglyceride levels steadily decreasing from 32.3 to 3.18 mmol/l and remained so throughout the treatment. There was no side effect observe at this period of treatment.

DOI: 10.1530/endoabs.37.EP1280

EP1281

Multiple endocrine organ failure due to amyloidosis

Feyzi Gokosmanoglu, Cigdem Tura Bahadir, Elif Kilic Kan & Aysegul Atmaca
Ondokuz Mayis University, Samsun, Turkey.

Introduction
Amyloidosis is characterised by accumulation of amorph and proteinous substance in several tissues and organs. Thyroid, adrenal, and pituitary insufficiencies may rarely be observed due to accumulation of these substances. Here, we present a case to point out this rare condition.
Case report
A 19-year-old male patient admitted with complaints of swelling in the neck, abnormality in thyroid hormone levels and fatigue. He had been diagnosed with familial Mediterranean fever at the age of 5. At 13 years old, he had renal insufficiency due to amyloidosis and had undergone renal transplantation. Physical examination revealed systemic arterial blood pressure of 90/60 mmHg, pulse rate of 72 beats/min. Thyoid gland was found to be diffuse palpable (grade 2), secondary sex characteristics development was defined as stages 2–3. In laboratory evaluation, TSH level was elevated, FT_4 level was decreased, anti-TPO and anti-TG were negative. He had primary adrenal insufficiency and hypogonadothrophic hypogonadism. ACTH and GnRH stimulation tests were in concordance with primary adrenal failure and hypogonadothrophic hypogonadism. Thyroid ultrasonography revealed that right thyroid lobe was $24\times23\times54$ mm and left thyroid lobe was $17\times21\times52$ mm in diameters. Isthmus was 5.5 mm in diameter and there was heterogenic echogenity in thyroid parenchyma. Doppler ultrasonography revealed grades 1–2 increased thickness in thyroid parenchyma. Thyroid fine needle aspiration biopsy revealed homogenous eosinophyllic accumulation which was stained histochemically with congo red and methyl violet between thyroid follicullar cells. Pituitary magnetic resonance imaging was normal. In the light of these findings the patient was diagnosed with amyloid goitre, primary adrenal insufficiency, and partial pituitary insufficiency. Prednisolone 5 mg/day, levothyroxine 50 μg/day, and testesterone enanthate 125 mg every 3 weeks were administered.
Conclusions
Systemic amyloidosis may be accompanied with amyloid accumulation in thyroid gland as well as adrenal and pituitary insufficiencies. Thus, endocrinologic evaluation is necessary in these patients.

DOI: 10.1530/endoabs.37.EP1281

EP1282

Gynaecomastia in a patient with von Recklinghausen's disease (neurofibromatosis type 1)

Ekaterina Sorkina[1], Liubov Machekhina[2], Aliy Asanov[1] & Konstantin Makhinov[1]
[1]I.M. Sechenov First Moscow State Medical University, Moscow, Russia; [2]Endocrinology Research Center, Moscow, Russia.

Introduction
Neurofibromatosis type 1 (NF1), also known as von Recklinghausen's disease, is the most common type of NF and one of the most frequent human genetic diseases. Gynaecomastia due to pseudoangiomatous stromal hyperplasia (PASH) in patients with NF1 is quite a rare complication but still it should be differentiated from gynecomastia caused by other conditions.
Clinical case
A 30-year-old man, previously diagnosed with NF1 at the age of 19, was first consulted in the Endocrinology department of MSMU in March 2014. He complained bilateral enlargement of breasts, painful feeling in them, weight loss, reduction of libido, muscle weakness, back pain and pain in the legs, diarrhoea. Physical examination: height 165 cm, weight 42.5 kg, BMI 15.7 kg/m^2, strong reduction of subcutaneous fat, breasts enlarged, painful while palpated; loss of facial hair, multiple neurofibromas in supraclavicular, axillary, and parotid areas. Laboratory analysis: serum creatinine 50.8 mmol/l (62.0–115.0), prolactin 136 mIU/ml (47–135), macroprolactin 61 mIU/ml, estradiol 97 pmol/l (0–146), testosterone 9.7 nmol/l (8.4–28.7), and leptin 0.9 ng/ml (2–5.6). DXA: generalized osteoporosis (Z-criteria -3.2 to -3.8), Total body quantitation: total fat tissue 9.9%. Immunological tests of specific antibodies in celiac disease: negative. Brain MRI: no signs of a pituitary adenoma. Breasts US: gland tissue hyperplasia, ducts are not dilated, no cysts or tumours were detected. Mediastinum lymph nodes biopsy: neurofibromas. Spine CT, MRI: multiple neurofibromas. Neurologic status: Multiple compressive-ischemic mononeuropathies of upper and lower limbs, distal assymetric tetraparesis, neuropathic pain syndrome, crampy. Pain syndrome is treated successfully with pregabalin 375 mg/day and amitriptyline 0.05 mg/day. A bilateral mastectomy was performed at June 2014. Osteoporosis is treated with zoledronic acid and combined preparations of calcium and vitamin D3.
Conclusion
We report our experience of gynecomastia and hyperprolactinaemia in a patient with NF1. Though these are rare complications of the disease, if found, such patients should undergo complex examination to exclude other causes of this state, which can worsen the course of their primary disease.

DOI: 10.1530/endoabs.37.EP1282

EP1283

Petrified ears associated with Schmidt's syndrome

Ana Valea[1,2], Andra Morar[2], Maria Breaban[2], Florica Tomesc[2], Adina Terec[2], Iulia Iacob[2], Dan Dumitru Pop[2], Alina Silaghi[2] & Cristina Ghervan[1]
[1]University of Medicine and Pharmacy Cluj-Napoca, Cluj-Napoca, Cluj, Romania; [2]Endocrinology Department, Cluj-Napoca, Cluj, Romania.

Introduction
Bilateral calcification of auricular cartilage is an uncommonly reported condition. The aetiology of this phenomenon is still unclear. Petrified ears have seldom been described in association with endocrinopathies such as adrenal insufficiency, hypothyroidism, diabetes mellitus, and acromegaly.
Case report
We present the case of a 42 year-old male patient, diagnosed with Addison's disease at the age of 14, currently undergoing treatment with prednisone 10 mg/day, with low compliance and therefore repeated episodes of adrenal crisis throughout the years. At the age of 42 he was diagnosed with hypothyroidism due to Hashimoto's thyroiditis and treatment with levothyroxine 25 μg/day was initiated. Physical examination revealed hyperpigmentation of the skin, lipoma of the posterior chest wall, markedly rigid auricular cartilages that were difficult to fold manually, with no evidence of hearing impairment. CT scan confirmed bilateral calcification of the auricular cartilages.
Conclusions
A long history of poorly controlled adrenal insufficiency (in this case more than 25 years) and the presence of primary hypothyroidism seem to be precipitating factors for auricular calcification.

DOI: 10.1530/endoabs.37.EP1283

EP1284

Two cases of bullous pemphigoid induced by vildagliptin

Asli Dogruk Unal, Ozlem Tarcin, Gulsen Tukenmez Demirci, Ebru Demiralay, Ayse Tulin Mansur, Semsi Yildiz & Nilgun Guvener Demirag
Baskent University Hospital, Istanbul, Turkey.

Background
Bullous pemphigoid is an autoimmune blistering disease that commonly arise in elderly with increased risk for mortality and morbidity. The aetiology of this disease is not entirely clear, although a few cases have been described with dipeptidyl peptidase IV inhibitors.
Case 1
A 81-year-old man presented with bullous pemphigoid after 28-month treatment with repaglinide, vildagliptin, and metformin. The patient's condition didn't improve with local treatment with clobetasol. The patient was started on methylprednisolone and azathiopurine but skin lesions sustained. Remission was achieved only after withdrawal of gliptin.
Case 2
A 64-year-old man treated with insulin glargine, insulin aspart, and vildagliptin for 12 months presented with bullous pemphigoid on skin and laryngeal mucosa. After discontinuation of vildagliptin skin lesions were resolved but laryngeal involvement continued. Mucosal lesions were resolved after methyprednisolone and azothiopurine treatment.
Conclusion
In the literature, there have been few cases descibed with gliptins. The exact mechanism has not been known but believed to be modified immune responses. These reports support the risk of bullous pemphigoid in patients exposed to gliptins. The difference of our cases from the literature is mucosal involvement and remission of our cases only with immunosuppressive agents.

DOI: 10.1530/endoabs.37.EP1284

EP1285

Hashimoto's thyroiditis with subclinical hypothyroidism, but severe growth delay in a prepubertal boy

Emilia Ghita, Alina Andreea Gatu, Voichita Mogos & Dumitru Branisteanu
Department of Endocrinology, University of Medicine and Pharmacy 'Gr.T. Popa', Iasi, Romania.

Hashimoto's thyroiditis is an autoimmnune condition most common in females but can be also found in children with a prevalence of 1.2%. When is associated with hypothyroidism, the growth delay is an important, but late symptom. We present the case of a 12-year-old boy presenting with small height for age (123 cm, < -3 S.D.), important weight gain and fatigue. He was the only child from parents of average height and had normal weight at birth (3300 g). Growth delay was not obvious until 2–3 years ago, when the child remained the shortest in the class, growing at a pace of < 2 cm/year. Although with an IQ above average, the patient had mild features of hypothyroidism. Clinical supposition was confirmed by laboratory investigation: $fT_4 = 0.3$ ng/ml (normal 0.9–1.9 ng/ml) and TSH = 35 mIU/l (normal 0.4–6 mIU/l). Etiological diagnosis of atrophic Hashimoto's thyroiditis was set by high titers of anti-peroxidase antibodies – 326 U/l (positive when > 50 U/l) and small, hypoechogenic, avascular thyroid gland. Therapy with 100 μg/day L-thyroxine and daily rGH injections (0.035 mg/kg per day) was initiated, with spectacular catch-up growth of 30 cm in 2 years (153 cm at 13 years, -0.8 S.D., corresponding to adult parental height). Hashimoto's thyroiditis is a frequent disease in adult women, but seldomly encountered in prepubertal boys. Normal intellect, relatively harmonious development and the presence of the thyroid gland excluded the hypothesis of an undiagnosed congenital myxoedema in our case. Diagnosis was mainly set by severe growth delay. Catch-up growth under thyroid hormone substitution does not completely restore height handicap in long-standing hypothyroidism, therefore the association of GH therapy may be beneficial, as in our case.

DOI: 10.1530/endoabs.37.EP1285

EP1286

A case of childhood autoimmune polyglandular syndrome type 1

Aysegul Alpcan[1], Bilge Eris[2], Senay Arikan Durmaz[3], Aydin Cifci[2] & Isilay Kalan[3]
[1]Kirikkale Yuksek Ihtisas Hospital, Kirikkale, Turkey; [2]Department of Internal Medicine, Kirikkale, Turkey; [3]Department of Endocrinology and Metabolism, Kirikkale University, Kirikkale, Turkey.

Autoimmune polyendocrine syndromes (APS) are rare groups of diseases with autoimmune failure of at least two endocrine glands. In general, APS1 first occurs with candidiasis. Hypoparathyroidism generally presents until 10 years of age, and adrenal insufficiency around 20 years. We aim to this report a young girl is presented with early onset APS1 first presenting with adrenal insufficiency.
Mucocutaneous candidiasis on the oral mucosa, and ectodermal dystrophic changes in her nails attracted attention in an 18-year-old girl in asthenic appearance who attended the Endocrinology Outpatient Clinic for malaise and failure to thrive. No hyperpigmentation was detected on the skin and mucosa on physical examination because she took corticosteroid treatment. Pubertal development was accordant with Tanner stage 5.Other systemic examinations were normal. It was learned from her anamnesis that malaise, loss of appetite, darkening in skin colour, and changes in the nails were first detected and investigated at a Paediatrics outpatient clinic she attended when she was 6 years old. As much as learned from her records at that time, her height and weight were consistent with her age, turgor was decreased, the skin was dry, there were marking, shape and color changes in the hand nails, candidiasis and skin hyperpigmentation were detected. As PTH was 2.83 pg/ml (15–65), ACTH was 1250 pg/ml (7.2–63.3), and basal cortisol was 1 μg/dl (6.2–19.4), and there was no response to Synacthen stimulation test. Adrenal insufficiency, hypoparathyroidism, and candidiasis were detected and the patient was diagnosed for APS1.
Conclusion
APSs clinically include a quite broad group of diseases. When one type of endocrinological disease is detected in a patient, the patient should be tested for complete blood count, electrolytes, hormonal levels, and antibodies for other diseases once every 3 years.

DOI: 10.1530/endoabs.37.EP1286

EP1287

Propylthiouracil-induced hepatotoxicity in Graves' disease: a case report

Hela Marmouch[1,2], Sondes Arfa[1], Tesnim Slim[1], Fadia Boubaker[1], Hanene Sayadi[1,2], Manel Jmal[1,2] & Ines Khochtali[1,2]
[1]Department of Internal Medicine–Endocrinology, Monastir, Tunisia; [2]Faculty of Medicine, Monastir, Tunisia.

Introduction
Propylthiouracil-induced severe hepatotoxicity is a relatively rare occurrence, with very few cases reported in the literature. The management of this complication in pregnancy can be a challenge because of the effects of the various treatment options on the foetus.
Case presentation
We report a case of hyperthyroidism in a 28-year-old woman that occurred at 20 weeks gestation. This situation was due to Graves' disease. Propylthiouracil treatment was used. The following of the pregnancy doesn't shows any side effects. 15 days after delivery, she has a vomiting and fatigue. Check list show elevated ALAT = 1000 UI/l. This liver toxicity has been managed by stopping this medication. After 4 days, ALAT romain to normal rate.
Conclusion
This case illustrates a rare complication of treatment with a presumed safe drug during pregnancy followed by adverse maternal outcomes due to the hepatotoxicity treatment.

DOI: 10.1530/endoabs.37.EP1287

EP1288

Combined treatment with sitagliptin and vitamin D in a patient with latent autoimmune diabetes of adulthood

Eleni Rapti, Athanasios Mousiolis, Maria Grammatiki, Maria Yavropoulou, Pantelis Zebekakis, Michail Daniilidis & Kalliopi Kotsa
University General Hospital of Thessaloniki AHEPA, Thessaloniki, Greece.

Objective
To report a case of a patient diagnosed with latent autoimmune diabetes of adulthood (LADA) based on clinical presentation and positive glutamic acid decarboxylase antibodies (GAD-abs) that converted to antibody negative diabetes after combined treatment with sitagliptin and vitamin D.
Methods
A 31-year-old male presented at the emergency room with symptoms of polyuria, polydipsia, and weight loss. Blood glucose was 300 mg/dl with mild ketonuria and HbA1c was 9.6%. The patient had a family history of autoimmune disorders. Declining insulin therapy he was initially treated with gliclazide and metformin. Owing to the patients poor glycemic control a GAD-abs titer measurement was performed and the results came back positive at 32 U/ml (NV <5 U/ml), so a LADA diagnosis was established. Other blood tests came back normal except from a low 25-OH-vitD level of 11 ng/ml (NV >30 ng/ml). Declining insulin therapy, he was advised to discontinue gliclazide and a combination of metformin 850 mg/sitagliptin 50 mg twice daily along with vitamin D supplementation (2000 IU/day) was prescribed.
Results
At follow-up visits, his HbA1c was 6.1% at 6 months and 5.4% at 11 months. His GAD-abs level declined by 86% within normal range at 4.2 U/ml. Two years later, receiving the same treatment, he has negative GAD-abs, his HbA1c is 5.2% and he maintains an excellent glycaemic profile.
Conclusion
Both vitamin D analogues and dipeptidyl peptidase 4 (DPP4) inhibitors have been shown to improve β-cell function and attenuate autoimmunity in type 1 diabetic mouse models. To our knowledge this is the first case that combined treatment with sitagliptin and vitD in a patient with LADA reverted the phenotype and preserved an excellent glycaemic control without the use of insulin 24 months after diagnosis.

DOI: 10.1530/endoabs.37.EP1288

EP1289

A rare case of papillary thyroid carcinoma and MALT thyroid lymphoma in the setting of Hashimoto's thyroiditis

Nada Santrac[1], Merima Oruci[1], Marko Buta[1], Igor Djurisic[1], Emilija Golubovic[1], Gordana Pupic[2] & Radan Dzodic[1,3]
[1]Surgical Oncology Clinic, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia; [2]Department of Pathology, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia; [3]Medical School, University of Belgrade, Belgrade, Serbia.

Introduction
Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy (80%), while primary thyroid lymphomas (PTL) occur in only 0.6–5% of cases. A significant number of PTCs, as well as PTLs, arise in the setting of Hashimoto's thyroiditis (HT), however the simultaneous occurrence of these two malignancies is extremely rare.
Case report
We present a 34-year-old female patient with thyroid MALT lymphoma and coexisting papillary microcarcinoma (PMC) in the setting of HT in the contralateral lobe that was admitted to our Institution for thyroid surgery. Patient had no compressive symptoms or lymphoma-related symptoms. Physical and ultrasonical examination in our Institution showed euthyroid multinodal goitre with pre-laryngeal medial neck mass (position of pyramidal lobe) and negative regional lymph nodes. Additionally, patient had increased antibodies' level. Preoperative fine-needle aspiration biopsy of pyramidal lobe tumour showed HT. Patient was submitted to total thyroidectomy with sentinel lymph node biopsy of jugulo-carotid regions after 1%-methylene blue dye injection. Histopathology analysis showed MALT lymphoma in the right lobe and HT with incidental PMC in the left lobe. Lymph nodes were diagnosed as benign, with reactive sinus histiocytosis. Postoperative whole body scintigraphy with radioiodine 131 was negative and substitutional-suppressive therapy with levothyroxine was initiated. Complete multidisciplinary diagnostic evaluation for MALT lymphoma was performed with confirmation of PTL stage IE, thus no further therapy was conducted. Ten months after surgery, presented patient is without recurrence.
Conclusions
Optimal management of coexisting PTC and MALT lymphoma depends on stage of both diseases at the initial presentation. In patients with HT, attention should be focused on frequent concomitant PTCs and possible occurrence of lymphomas, thus total thyroidectomy represents a therapy of choice.

DOI: 10.1530/endoabs.37.EP1289

EP1290

Nephrogenic syndrome of inappropriate antidiuresis secondary to an activating mutation in the arginine vasopressin receptor AVPR2

Andrew S Powlson[1], Benjamin G Challis[1], Alice Lagnado[1], David J Halsall[2], Robert K Semple[1] & Mark Gurnell[1]
[1]Metabolic Research Laboratories, Institute of Metabolic Science, University of Cambridge, Cambridge, UK; [2]Department of Clinical Biochemistry, Addenbrooke's Hospital, Cambridge, UK.

Case history
A 38-year-old man was referred with a 12-month history of recurrent bouts of transient hyponatraemia (serum sodium ranging from 115 to 125 mmol/l). Citalopram, which he was taking for depression, was discontinued, but the episodes continued.
Initial investigations
Whilst symptomatic, and clinically euvolaemic, his biochemical profile was consistent with a syndrome of inappropriate antidiuresis (SIAD): sodium 124 mmol/l, potassium 4.5 mmol/l, glucose 6 mmol/l, urea 4.7 mmol/l, creatinine 76 μmol/l, serum osmolality 268 mOsm/kg, urine osmolality 652 mOsm/kg, and urine sodium 154 mmol/l. A contemporaneous anterior pituitary profile, including short Synacthen test, was normal, as were urinary porphobilinogens. Head, chest, and abdominal CT were unremarkable.
Laboratory studies
A water load test was arranged: after 4 h he had excreted just 15% of a 20 ml/kg oral load (normal range 78–82%) and his serum sodium fell from a baseline of 134 mmol/l to a nadir of 125 mmol/l (serum osmolality 266 mOsm/kg and urine 808 mOsm/kg), consistent with inappropriate antidiuresis. Despite this, his AVP levels were profoundly low (0.4–0.9 pmol/l) throughout the test, indicating a nephrogenic syndrome of inappropriate antidiuresis. Sanger sequencing of *AVPR2* revealed a missense mutation (X-linked) in a highly conserved arginine residue in the second intracellular loop (R137C). The mutant receptor exhibits constitutive activity when compared with its WT counterpart in transient transfection assays.
Discussion
Confirmed cases with activating mutations in AVPR2 causing nephrogenic SIAD are rare, with only sixteen cases reported worldwide since the syndrome was first described in 2005. However, this disorder may be underdiagnosed, based on historical reports of AVP levels in unexplained hyponatraemia. The ability to find a definitive cause in this case has provided validation to our patient, given a rational for preventative management with fluid restriction, and allows the potential for family screening.

DOI: 10.1530/endoabs.37.EP1290

EP1291

Nephrotic syndrome due to membranous nephropathy as the cause of rising TSH levels or primary hypothyroidism as the cause of nephrotic syndrome? A case report

Sohini Patel[2], Nirav Gandhi[1,2] & Jayadave Shakher[1]
[1]Birmingham Heartlands Hospital, Birmingham, UK; [2]University of Birmingham, Birmingham, UK.

We present a case of a 52-year-old man with a past medical history of primary hypothyroidism on treatment, presenting with elevated TSH levels, suggesting inadequate thyroxine (T_4) replacement. The patient was managed with 200 μg of T_4 for 14 years with no compliance issues. TSH levels failed to normalise despite increasing the dose of T_4. In addition to elevated TSH levels the patient noted progressive leg swelling and associated shortness of breath over the preceding 12 months. Examination revealed bilateral pitting oedema up to the abdomen and elevated blood pressure (175/103 mmHg). Initial blood results demonstrated a low albumin of 21 g/l, down from a previous 44 g/l with urinalysis confirming marked proteinuria ($+3$) in addition to blood ($+2$). Subsequently, nephrotic syndrome was investigated as a probable cause. Twenty-four hour urinary protein was raised at 12.42 g (normal <0.15 g). A kidney biopsy was performed which demonstrated membranous glomerulonephritis. The nephrotic syndrome was

symptomatically managed on frusemide 40 mg b.d. and ramipril 10 mg o.m. The proteinuria improved with reduction of peripheral oedema and stabilization of TSH levels. There are numerous causes of elevated TSH levels in a primary hypothyroidism patient on T_4. One of the less commoner causes is nephrotic syndrome, characterized by oedema, hypoalbuminaemia and proteinuria. Increased glomerular permeability results in loss of thyroxine-binding globulin (TBG) and free T_3/T_4. As a result, the pituitary–hypothalamic axis responded by increasing TSH production to compensate for reduced serum T_3/T_4. This elevation of TSH is not responsive to increasing doses of exogenous T_4 due to urinary loss of TBG. Management is of the underlying nephrotic syndrome. It is important to recognise that many hormones are protein based, as are their carrier molecules calling for a closer analysis of symptoms on presentation of elevated TSH.

DOI: 10.1530/endoabs.37.EP1291

EP1292

Clinical case: gender identity disorder as an aetiology of hypothalamic amenorrhoea

Natalia Volkova, Maria Porksheyan & Saida Kanaeva
Rostov State Medical University, Rostov on Don, Russia.

Hypothalamic amenorrhoea is a diagnosis of exclusion, frequent cause of which are medications or psychiatric disorders (bulimia/anorexia). Here we present a case, when its aetiology was gender identity disorder. A 18-year-old girl presented with absence of menses during last year. Menses began at the age of 14 and were regular till age of 16, when she moved to another city. She was seen by gynaecologist because of amenorrhea, and evaluation was performed: FSH 4.6 mU/ml (1.37–9.9), LH 7.2 mU/ml (1.68–15.0), oestradiol 20 pg/ml (68–606), total testosterone 0.5 nmol/l (0.38–1.97), TSH 2 mU/l (0.4–4.0), prolactin 570 mU/l (109–557), and US, multifollicular ovaries. 'Ovarial hypofunction' was established, and vitaminotherapy was prescribed without any effect. She appealed to different specialists, however, definitive diagnosis wasn't established. At the age of 17, menses were recovered spontaneously and stopped again in 6 months. Patient had not taken OC, weight remained stable. Physical examination revealed BMI 19 kg/m^2, hirsute number 0, breast development Tanner 5. Hormonal test results were in reference range, hCG was negative. Talking with patient, our attention was drawn by her hysterical behaviour, because she told about herself as an asexual being. Thereby, she appealed to psychiatrist, and diagnosis of gender identity disorder was established. It was interesting to note that her menses recovered at that time, when she fell in love and felt as a woman. Taking into consideration absence of pregnancy, excluded endocrine causes of amenorrhea, no history of OC, no excess or insufficient food intake, spontaneous menses recover during normal identity, there was established diagnosis of hypothalamic amenorrhoea, and psychiatric treatment was recommended. In case of amenorrhoea, body weight changes, and careful inspection are needed while suspicion of bulimia/anorexia. It is also needed to pay attention to patient's speech, which may be a clue to diagnosis of gender identity disorder as a cause of hypothalamic amenorrhea.

DOI: 10.1530/endoabs.37.EP1292

EP1293

Multiple endocrine neoplasia type 2A in a Turkish family presented with nonspesific symptoms

Dilek Tuzun[1], Ayten Oguz[1], Murat Sahin[1], Ilhami Taner Kaleli[2], Sevgi Bakaris[3], Mustafa Saygin Deniz[4], Cansu Yilmaz Cabioglu[4] & Kamile Gul[1]
[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey; [2]Department of General Surgery, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey; [3]Department of Pathology, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey; [4]Department of Internal Medicine, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey.

Introduction
Multiple endocrine neoplasia type 2A (MEN2A) is a complex autosomal dominant inherited syndrome characterized by medullary thyroid carcinoma (MTC), phaeochromocytoma, and primary parathyroid hyperplasia (PPH). In patients with only one or two clinical features, identification of a germline rearranged in transfection (RET) mutation or the identification of the clinical features of MEN2A in other first degree relatives is required to make the diagnosis. We present the case of a family with MEN2A syndrome, diagnosed with the complaint of abdominal pain.
Cases
Index case was the brother – OS – aged 28 years and was admitted to the hospital with the complaint of abdominal pain. There was no pathology in his medical history and physical examination. In radiologic examination; bilateral adrenal adenoma, multinodular goitre (MNG) and PPH was detected. Fine-needle aspiration cytology (FNAC) revealed MTC. And then operated for MTC, phaeochromocytoma, and PPH. Genetic analysis showed RET gene mutation in 634codons. His father was died from myocardial infarction 5 years ago. Upon that all family members were investigated for MEN. Second case (brother, GS, aged 27 years), third case (sister, AK aged 32 years), and fourth case (sister, LK, aged 22 years) had also MNG in thyroid USG examination, PPH and FNAC revealed MTC. Operations also decided for them. Biochemical and hormonal parameters of cases are as shown in Table 1.

Table 1

	Case 1, OS	Case 2, GS	Case 3, AK	Case 4, LK	Normal reference range
PRA	5,82	11	21.07	42	0.7–3.3 ng/ml per h
PAC	2.37	0.78	4.46	4.68	7–30 ng/dl
Normetanephrine (urine)	1054	3401	1120	1227	88–444 μg/day
Metanephrine (urine)	3211	14527	1831	3108	52–341 μg/day
Cortisol	15	15	18	22	5–25 μg/dl
TSH	2.2	1.18	2.86	0.9	0.4–4 IU/ml
DHEAS	215	150	148	155	35–560 μg/dl
Calcitonin	622	132	40	698	<18.2 pg/ml (men) and <11.5 pg/ml (women)
Parathormone	145	91	87	121	10–65 pg/ml
Calcium	11.5	11	10.3	10.4	8.4–10.2 mg/dl
Albumin	4.2	4.3	4.3	4.7	3.5–5.2 g/dl
Phosphor	2.6	3.6	4.1	3.7	2.4–5.4 mg/dl
1 mg overnight DST cortisol	1.3	0.9	1.4	1.31	<1.8 μg/dl

PRA, plasma renin activity; PAC, plasma aldosterone concentration; DST, dexamethasone suppression test.

Discussion
MEN2A is the most prevalent form and presents with MTC in 95% of cases, bilateral pheochromocytoma in 50% of the cases and primary hyperparathyroidism in 25% of cases. Bilateral adrenal adenoms determined at a young age should be investigated interms of MEN syndrome. Also, in our index case bilateral adrenal adenoms were incidentally detected. In light of the association between certain familial syndromes and patients diagnosed with pheochromocytomas at a young age should be screened with genetic testing for a RET mutation.

DOI: 10.1530/endoabs.37.EP1293

EP1294

Cervical paraganglioma ultrasonographically mimicking parathyroid adenoma: a case report

Selvihan Beysel[1], Mustafa Caliskan[1], Muyesser Sayki Arslan[1], Melia Karakose[1], Esra Tutal[1], Seyfullah Kan[1], Muhammed Kizilgul[1], Mahmut Apaydin[1], Erman Cakal[1], Mustafa Ozbek[1] & Tuncay Delibasi[1,2]
[1]Department of Endocrinology and Metabolism, Diskapi, Teaching and Research Hospital, Ankara, Turkey; [2]School of Medicine (Kastamonu), Hacettepe University, Ankara, Turkey.

Introduction
Paragangliomas are neuroendocrine tumors arising from extra-adrenal chromaffin cells. Paragangliomas of the head and neck frequently originate from the paraganglionic system including the carotid bifurcation, middle ear and the ganglion nodosum of the vagus nerve. However, of paragangliomas of the head and neck, only 1–3% secrete hormones and majority are non-functional. Here, we describe a case of non-functional paraganglioma confused with parathyroid adenoma ultrasonographically.

Case
A 45-year-old female patient attending to our department with difficulty in swallowing was found to have a palpable mass lesion in the right lower cervical region. A neck ultrasound showed a hypo-echoic, solid lesion without increased vascularity (15×18×24 mm) adjacent to the capsule of the lower pole of the thyroid lobe. She was euthyroid and had normal calcium and parathyroid hormone levels. Its location adjacent to the thyroid capsule suggested a non-functional parathyroid lesion. Thus, a technetium sestamibi scanning did not demonstrate any activity uptake consistent with a parathyroid lesion. Also a neck exploration was performed for differential diagnosis. Encapsulated solid nodule was confirmed a benign paraganglioma by histopatologic examination. Hormonal profile revealed a serum menanephrine of 0.37 nmol/l (*n*: 0.08–0.51), serum normetanephrine of 1.24 nmol/l (*n*: 0.12–1.18), urinary menatephrine of 78.29 µg/day (*n*: 52–341), and a urinary normetanephrine of 221.8 µg/day (*n*: 88–444). Thus, a diagnosis of non-functional paraganglioma was established, and further radiological imaging did not reveal paragangliomas at other sites.
Conclusion
Herein, we reported a case of cervical non-functional paraganglioma located at the neck that can be confused with a parathyroid adenoma ultrasonographically. In normocalcaemic patients with normal parathyroid hormone levels, a diagnosis of cervical paraganglioma should also be considered due to its ultrasonographic similarity to parathyroid lesions.

DOI: 10.1530/endoabs.37.EP1294

EP1295

Concurrent mediastinal parathyroid carcinoma and parathyroid adenoma

Mustafa Caliskan, Selvihan Beysel[1], Esra Tutal[1], Bekir Ucan[1], Taner Demirci[1], Seyfullah Kan[1], Mahmut Apaydin[1], Muhammed Kizilgul[1], Guleser Saylam[2], Erman Cakal[1], Mustafa Ozbek[1] & Tuncay Delibasi[1,3]
[1]Department of Endocrinology and Metabolism, Diskapi Teaching and Research Hospital, Ankara, Turkey; [2]Department of Otorhinolaryngology, Diskapi Teaching and Research Hospital, Ankara, Turkey; [3]School of Medicine (Kastamonu), Hacettepe University, Ankara, Turkey.

Introduction
While mediastinal parathyroid carcinoma is a rare entity by itself, multiglandular coexistence of parathyroid carcinoma and adenoma represents an extremely rare condition. Herein, we report such a rare presentation of multiglandular parathyroid neoplasm with an ectopic carcinoma in the mediastinum and adenoma on the right side of neck in a patient with persistent primary hyperparathyroidism (PHP).
Case report
A 38-year-old female patient who initially presented with nephrolithiasis and osteopenia was subsequently diagnosed as having PHP. Tc-^{99m}-methoxybutylisonitrile scintigraphy showed no parathyroid lesions, while a neck ultrasound determined the presence of a solid hypoechoic nodular lesion (4×4×8 mm) at the postero-inferior aspect of the right thyroid lobe. Following bilateral surgical neck exploration, existence of a parathyroid adenoma was revealed. However, due to the persistence of hypercalcaemia postoperatively, a single photon emission computed tomographic examination showed a mass lesion in the anterior mediastinum and no lesion in the neck region. A second surgical procedure was performed and histopathological examination revealed the presence of a mediastinal parathyroid carcinoma with evidence of invasion in the capsule and surrounding adipose tissue, without metastatic lymph nodes. At 1-year of follow-up there was no hypercalcaemia. The chest computed tomography failed to demonstrate any lesions in the mediastinum and neck region.
Discussion
To our knowledge, only four cases have been described in the literature with concurrent occurrence of multiglandular parathyroid adenoma and carcinoma, with all cases having the multiglandular parathyroid carcinoma localised in the neck. This is the first patient who had coexistent ectopic mediastinal parathyroid carcinoma and parathyroid adenoma in the neck with persistent PHP.
Conclusion
Concurrent occurrence of ectopic mediastinal parathyroid carcinoma and parathyroid adenoma may be result in significant diagnostic challenges for the clinicians. Multiple diagnostic studies appear to be required and essential for the identification of multiple parathyroid glands in patients with persistent PHP.

DOI: 10.1530/endoabs.37.EP1295

EP1296

Radioguided excision of occult metastatic lesion in thyroid carcinoma: a safe technique for previously operated neck in two patients

Teresa Martins, Teresa Azevedo, Jacinta Santos, Fernando Rodrigues, Eugenia Rovira, Sofia Oliveira, João Neto, António Neves, Patricia Gilde & Carlos Cruz
Portuguese Institute of Oncology, Coimbra, Portugal.

Introduction
Intraoperative identification of neck lesions in patients who have undergone previous neck surgery is particularly difficult, because of operative scarring and distorted anatomy. Radioguided occult lesion localisation (ROLL) involves the preoperative intratumoral ultrasound-guided injection of a radioactive tracer. In the present study, we investigated the efficacy of roll in two patients with papillary thyroid cancer (PTC) who underwent previous neck exploration.
Material and methods
This study included two patients with recurrent/persistent PTC who have previously undergone operation. Patient 1: female, 65 years with PTC (T1bN1bM0) previously operated in 2010 with recurrence in the central neck (nodule with 9×7 mm). A fine-needle aspiration (FNA) cytology with FNA thyroglobulin (Tg) measurement was performed and confirmed the diagnosis of malignancy; patient 2: male, 50 years with PTC (T4aN1bM0) previously operated four times with three nodules in the central neck with 9, 7, and 6 mm. The largest nodule was submitted to FNA cytology confirming recurrence. In both patients ^{99m}TC-labeled macroaggregated albumin was injected directly into each lesion under US guidance 90 min before surgery. Scintigraphy was performed 30 min after injection to visualize the focally increased uptake of radiotracer. Intraoperative lesion detection was performed with gamma probe by identifying areas of maximum radioactivity.
Results
In patient 1 the lesion was identified and excised but in the patient 2 only two lesions were identified and excised. Histopathological examination confirmed recurrence of PTC in all of the nodules excised. In patient 1 serum Tg dropped from 15 to <2 ng/ml but in patient 2 Tg didn't drop significantly and in the follow-up persisted a 7 mm nodule in the central neck.
Discussion
The Roll technique was efficient and safe in the perioperative identification of recurrent thyroid cancer in the central neck. This technique might help decrease the complications rates associated with reoperation.

DOI: 10.1530/endoabs.37.EP1296

EP1297

Familial hypocalciuric hypercalcaemia: case report

Ana Carolina Neves[1], Teresa Rego[1], Branca Cavaco[2], Fernando Fonseca[1] & Ana Agapito[1]
[1]Endocrinology Department, Curry Cabral Hospital – CHLC, Lisbon, Portugal; [2]Molecular Pathobiology Investigation Unit, Portuguese Oncology Institute, Lisbon, Portugal.

Introduction
Familial hypocalciuric hypercalcaemia (FHH) is a rare genetically heterogeneous disorder, with 3 variants described. An inactivating mutation in the calcium sensor receptor (CASR) gene causes the subtype 1, which represents 65% of the cases.
It is charaterised by hypercalcaemia and hypocalciuria with normal or elevated PTH. FHH is generally assymptomatic and treatment is not needed. Differential diagnosis with primary hyperparathyroidism (PHPT) is crucial and based on calcium-creatinine clearance ratio (CCCR), which, when under 0.02 points to the diagnosis of FHH. Genetic test is necessary for confirmation.
Case report
An assymptomatic 16-year-old girl was referred to Endocrinology Department due to hypercalcaemia. Family history of several malignancies was present. Her mother died at 39 years old from hepatocellular carcinoma, her maternal-aunt at 13 from sarcoma and her maternal cousin at 18 from ovarian carcinoma. Laboratory work-up: Ca 11.5 mg/dl (8.8–10.4); P 3.1 mg/dl (2.5–4.5); Ca(u) 92 µg/24 h (20–90); PTH 32 pg/ml (10–70); creatinine 0.7 mg/dl; and CCCR 0.007. DNA sequence analysis of *CASR* gene identified a frameshift mutation in exon 7, (c.1945delG), in heterozigoty, not previously described. Her father and half-brother had normal Ca and PTH levels. Some months later, patient maternal grandmother was observed for multinodular goitre and laboratory work-up

revealed Ca 11.9 mg/dl, P 3.1 mg/dl, PTH 93 pg/ml, 25OHD3 21.8 ng/ml (30–100), and Ca(u) 86 mg/24 h. Genetic study confirmed the same mutation.
Conclusions
FHH is a benign condition that must be considered in the differential diagnosis of hypercalcaemia with normal or elevated PTH. CCCR is used to distinguish it from PHPT, however the definitive diagnosis demands genetic study, in order to avoid needless parathyroidectomy. In this family, a novel mutation in *CASR* gene was identified.

DOI: 10.1530/endoabs.37.EP1297

EP1298

It is a link between Hashimoto encephalopathy and CLIPPERS syndrome?

Krzysztof Marczewski[1,2], Iwona Ciuba[1], Bozena Jarosz[3] & Dorota Boniek-Poprawa[1,2]
[1]Pope John Paul II Regional Hospital, Zamosc, Poland; [2]Zamosc University of Management and Administration, Zamosc, Poland; [3]Department of Neurosurgery and Pediatric Neurosurgery, Medical University of Lublin, Lublin, Poland.

Introduction
Different forms of brain damages in endocrine disease are relatively common. Recently the Hashimoto encephalopathy is more frequent recognised and successfully treated. The diagnosis criteria and treatment options however are still under discussion. On the other hand in neurology are described new pathologic entities, which can occurred also by endocrine patients.
Case
In September 2009 by the 66 years old women with type 2 diabetes and metabolic syndrome was diagnosed hypothyroidism in course of autoimmune thyroiditis with moderately elevated antithyroid antibodies. The hypothyroidism was successfully treated with levothyroxine, but in December 2012 patient was admitted with cognitive decline and impaired mobility. In CT brain metastases are described but the primary focus are not founded. In brain biopsy was found inflammatory infiltration from the T and B lymphocytes and macrophages, reactive gliosis and loss of myelin. After steroids, initially as pulses of 1 g methylprednisolone and then oral prednisonum (60 mg with subsequent reduction) clinical status was improved and in MRI we observed brain damage regressions until almost complete in November 2013. In May 2014 when attempting to further reduce the dose of steroids visual loss occurred on the right eye. The vision returned after pulses of methylprednisolone, which we have repeated in subsequent months. The patient is currently in a stable condition on oral 25 mg prednisone. Diabetes and hypothyroidism are treated effectively. She sees and moves quite well, although she had a depressed mood.
Comments
We have serious doubts regarding the diagnosis. The clinics including a strong dependence on steroids would speak rather for Clippers syndrome, but we cannot exclude pathology associated with thyroiditis, despite the relatively low titre of antibodies. Therefore, we would like to introduce our problem, to the European Endocrinologists in hope for comments and advice.

DOI: 10.1530/endoabs.37.EP1298

EP1299

Graves' orbitopathy coursing with hypothyroidism: a case-report

Ana Saavedra[1,2], Joana Menezes Nunes[1,2], Elisabete Rodrigues[1,2,3], Sara Ribeiro[4], Victor Leal[4] & Davide Carvalho[1,2]
[1]Department of Endocrinology Diabetes and Metabolism, Centro Hospitalar S. João, Porto, Portugal; [2]Faculty of Medicine, University of Porto, Porto, Portugal; [3]Instituto de Investigação e Inovação em Saúde, University of Porto, Porto, Portugal; [4]Department of Ophthalmology, Centro Hospitalar de São João, Porto, Portugal.

Introduction
Graves' orbitopathy is usually associated with Graves' Disease, which is typically characterized by hyperthyroidism and goiter. However, in rare situations, Graves' disease can also present with hypothyroidism and orbitopathy.
Case report
Male, 38 years old, followed by his ophthalmologist for thyroid orbitopathy (exophthalmos right > left and conjunctival hyperaemia since 1 year ago) associated with asthenia, tiredness and weight gain. He was referred to endocrinology consultation because he presented TSH elevated (62.75 μUI/ml, reference values (RV): 0.35–4.94) with normal FT_4 0.70 ng/dl (RV: 0.70–1.48) and normal FT_3 2.95 pg/ml (RV 1.71–3.71) and high levels of anti-thyroid and TSH-receptor autoantibodies (TRAbs) (5.2 U/l (RV: 0–1.8)). Thyroid ultrasonography showed a gland with normal dimensions, heterogeneous and pseudonodular texture, suggesting thyroiditis. The patient denied any previous treatment. He started therapy with levothyroxine and the dose was increased as needed. It was accompanied by improvement of hypothyroid symptoms. Six months later, he had normal TSH and TRAb's = 3.9 U/l (RV: 0–1.8). A year after starting therapy, symptoms reappeared and analytically he presented again with hypothyroidism (TSH = 14.71; FT_3 and FT_4N) and TRAB's levels > 40.0 U/l.
Discussion
It has been described in literature different types of TRAbs, which are capable of inducing two distinct clinical syndromes: thyroid-stimulating autoantibodies and TSH-blocking autoantibodies. In this patient with Graves's orbitopathy, a predominance of blocking type TRAbs vs stimulatory type may be a possible explanation for the presence of hypothyroidism. Although, we can't exclude the possible contribution, at least at some degree, from the gland's destruction (suggested by high titres of anti-peroxidase/anti-thyroglobulin autoantibodies and the findings suggestive of thyroiditis in ultrasound). Thus, the determination of TRAbs subtype is of particular interest in these less common forms of presentation of thyroid autoimmune pathology.

DOI: 10.1530/endoabs.37.EP1299

EP1300

Incidental thyroid cancer in a subcentimetric nodule with benign ultrasound criteria in a patient with Graves' disease

Enalda Demaj, Endri Ahmeti, Marjeta Kermaj, Violeta Hoxha, Gerond Husi, Thanas Fureraj, Dorina Ylli & Agron Ylli
Department of Endocrinology, University Hospital Center 'Mother Theresa', Tirana, Albania.

Introduction
A thyroid nodule discovered in a patient with Graves' disease (GD) should be evaluated and managed according to guidelines. A subcentimetre incidental thyroid cancer founded in a patients with GD, without high-risk history, without suspicious sonographic (US) features has not been reported yet.
Clinical case
A 40-year-old female patient, presented to our hospital with symptoms of thyrotoxicosis. On physical examination heart rate was 120 b.p.m., blood pressure of 130/90 mmHg, with a nontender thyroid gland, with murmurs on auscultation, without nodules on palpation. No exophtalmos or skin changes were noted. The patient was under treatment with methimazole 5 mg twice daily and β blocker, since 7 months. Laboratory investigations showed AST: 93 U/l, ALT: 156 U/l (*n*: < 40 U/l). Thyroid function tests revealed free T_3: 22.52 pg/ml (*n*: 2–4.4), free T_4: 63.04 ng/dl (*n*: 10.6–19.4), and TSH: 0.003 μUI/ml (*n*: 0.35–4.94). TRAbs: 1.8 UI/ml ($n < 1$). A thyroid ultrasound detected a diffuse enlargement with diffuse hypervascularity of thyroid, with a hyperechoic rounded nodule measuring 9 m ÷ 6.4 mm in the left lobe (with regular borders, with halo, without microcalcifications) and a hypoechoic right lobe. A scintigraphy showed a increased diffuse uptake, suggestive of GD. Fine-needle aspiration biopsy (FNAB) was not performed. Our patient underwent a total thyroidectomy after 2 months, in a euthyroid state. Histopatological examination of the thyroid gland showed a focus of papillary microcarcinoma, follicular variant, lying into the nodule detected on US.
Conclusions
Thyroid cancer occurs in GD patients with a frequency of 2% or less. We referred a case of incidental thyroid cancer in a Graves' disease with no malignant ultrasound features. We conclude that the presence of benign nodules on ultrasonographic examination does not reduce the risk of malignancy. We recommend a FNAB in all nodules detected on ultrasound in Graves' disease and early total thyroidectomy in these cases.

DOI: 10.1530/endoabs.37.EP1300

EP1301

Late onset of a rare autoimmune association: coeliac disease and Hashimoto's thyroiditis; hormonal and metabolic implications

Mirela Puiu[1], Radu Popa[2], Elena Gologan[3], Felicia Crumpei[4], Ioana Armasu[1], Ioana Vasiliu[1], Adina Manolachie[1], Cristina Preda[1] & Carmen Vulpoi[1]
[1]Department of Endocrinology, University of Medicine and Pharmacy 'Gr.T.Popa', Iasi, Romania; [2]Department of Vascular Surgery, University of Medicine and Pharmacy 'Gr.T.Popa', Iasi, Romania; [3]Department of Gastroenterology, University of Medicine and Pharmacy 'Gr.T.Popa', Iasi, Romania; [4]Department of Radiology and Medical Imaging, University of Medicine and Pharmacy 'Gr.T.Popa', Iasi, Romania.

Introduction
Several autoimmune determinations have been reported in association with autoimmune thyroidits (AIT). While the classical correlations with other endocrine or general autoimmune diseases like pernicious anemia or vitiligo are frequent and well defined, there are fewer data on other rarer associations, as with celiac disease (CD). In the absence of typical clinical symptoms this association may be overlooked, as in the case we present.
Case presentation
DM, 64 years old female patient, with three recent episodes of persistent diarrhea and weight loss, having negative bacteriologic and imagistic investigations (gastric endoscopy with antral biopsy, colonoscopy, and abdominal CT), was oriented to the Endocrine Department for hypothyroidism associated with severe diselectrolemia. On admission she presented asthenia, hypoanabolic syndrome (BMI 17.5 kg/m^2) and inferior limb edema. Biological data confirmed autoimmune thyroiditis with hypothyroidism (TSH = 27 μUI/ml, fT_4 = 0.7 ng/dl, ATPO > 1000 UI/ml, and ATg > 3000 UI/ml), inflammatory syndrome, severe vitamin D deficiency (< 3 ng/ml), and severe metabolic disturbances (hypoalbuminemia, hypokaliemia, hyponatremia, hypocalcemia, and acidosis). Markers for digestive neoplasia and NET were negative. Other investigations revealed osteoporosis and profound venous thrombosis with decreased tolerance to cumarinic anticoagulants (INR 7.32) which imposed heparinotherapy. Coeliac disease was suspected, sustained by positive antigliadin antibodies. Patient refused doudenal biopsy. Substitutive L-T_4 treatment, vitamin D supplementation and gluten-free diet was started, with rapid and persistent improvement of the general status and biological data.
Conclusion
Undiagnosed CD associated with TAI may determine severe metabolic disturbances due to the vicious circle of malabsorbtion. Low L-T_4 absorbtion impose attentive substitution dosage. Most of guides do not recommend systematic search of CD in TAI however, since, as in our patient, CD may be paucisymptomatic and/or with late manifestation, we believe that it may be useful to search it, if not in all AIT patients at least in those with metabolic disturbances.

DOI: 10.1530/endoabs.37.EP1301

EP1302

Malignant ectopic thyroid tissue with distant metastasis: a case report

Shehla Tabassum, Najmul Islam, Saulat Hasnain Fatimi, Mubasher Ikram, Arsalan Ahmed & Maseehuz Zaman
Aga Khan University, Karachi, Sind, Pakistan.

Introduction
Ectopic thyroid tissue is the most common form of thyroid dysgenesis. But primary malignant transformation in ectopic thyroid tissue is quite a rare entity, with follicular malignancy being the dominant form at ectopic sites. Very infrequently, malignant ectopic thyroid tissue can present with metastasis to lymph nodes. But we report a case of malignant ectopic thyroid tissue over manubrium sterni with distant metastasis.
Case presentation
A 42-year-old Pakistani female presented with gradually increasing swelling on anterior aspect of manubrium sterni for last 6 months. She had no goitre and was clinically and biochemically euthyroid. Rest of systemic exam was also unremarkable. CT chest showed a circumscribed soft tissue density mass arising from sternum, measuring 3.9×3.9 cm, causing erosions of anterior, right lateral and posterior walls of sternum. Trucut biopsy of the sternal mass proved it to be thyroid tissue with follicular differentiation and occasional mitotic figures. Multiple nodules were also noted in thyroid gland in US neck. She underwent total thyroidectomy and excision of ectopic thyroid tissue over manubrium sterni. Extensive histopathological examination of primary thyroid gland showed benign nodular hyperplasia with no evidence of malignancy. Ectopic thyroid tissue showed minimally invasive follicular thyroid carcinoma with tumor size of 3.2×2.3 cm. Her postoperative 21-day biochemical profile showed TSH 22.345 μIU/ml (0.4–4.2), serum thyroglobulin 88.3 ng/ml, and anti-TG antibodies < 20.0 IU/ml. Based on the histopatholigical diagnosis, she went through 30 mCi RAI-131 ablation. The post-ablative whole body scan showed good uptake of ablative dose over thyroid bed and evidence of multiple well-defined rounded areas of abnormally increased tracer accumulation over mid and lower dorsal spine, lumbar region and right iliac bone, representing bone metastasis. It was followed by MRI spine which showed foci of metastatic deposits in T1–T3 and L2 vertebral bodies and abnormal signals showing post-contrast enhancement in superior mediastinum with invasion of medial ends of both clavicles, more marked on right side. So patient was found to have malignant ectopic thyroid tissue with distant bone metastasis.
Conclusion
We describe the first case of its kind having malignant ectopic thyroid with metastasis to spine and ilium. Such cases may impose difficulties in their treatment decisions.

DOI: 10.1530/endoabs.37.EP1302

EP1303

Medullary thyroid carcinoma in multiple endocrine neoplasia 2A: a therapeutic challenge

Luis Cardoso[1], Dírcea Rodrigues[1,2], Gracinda Costa[2,3], Carolina Moreno[1,2], Daniela Guelho[1], Nuno Vicente[1], Margarida Balsa[4], Diana Martins[1], Diana Oliveira[1] & Francisco Carrilho[1]
[1]Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; [2]Faculty of Medicine, University of Coimbra, Coimbra, Portugal; [3]Department of Nuclear Medicine, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; [4]Department of Endocrinology, Centro Hospitalar do Baixo Vouga, Aveiro, Portugal.

Introduction
Medullary thyroid carcinoma (MTC) occurs in a hereditary pattern in 25% of cases. Virtually all patients with multiple endocrine neoplasia 2A (MEN2A) develop MTC. MTC aggressiveness and natural history varies according to the *RET* mutation. Prophylactic thyroidectomy may cure and/or prevent metastatic disease in most cases.
Case report
A 27-year-old man with past history of colostomy at 5 months of age for Hirschsprung disease and total thyroidectomy at age of 14 years old for the genetic diagnosis of MEN2A (C620R *RET*). Patient's underwent genetic study when his mother was diagnosed with MTC and a germline mutation in *RET* gene (C620R) was identified. Patient's post-operative histological diagnosis revealed two MTC foci of 1 and 0.3 cm. Patient was lost to follow-up at the age of 16. In the last year he reported low back pain radiated to right thigh. MRI showed a 9×5×8 cm mass in the right iliac bone and lesion biopsy was compatible with MTC metastasis. ^{68}Ga-DotaNoc PET showed uptake in the thyroid area, left parapharyngeal region, high density of somatostatin receptors in the left cervical region and right iliac bone. Biochemical analysis revealed thyroglobulin of < 0.2 ng/ml (1.6–60.0), calcitonin of 60.428 pg/ml (< 10), and CEA of 1.947 ng/ml (< 5.4). Patient underwent bilateral cervical lymph node dissection and subtotal resection of iliac metastasis. Histological examination confirmed MTC metastasis. Patient underwent a cycle of 200 mCi of ^{177}Lu-DotaTate, though low radionuclide uptake motivated its withdrawal. Patient showed increased uptake of ^{123}I-MIBG and treatment with ^{131}I-MIBG was started (154 mCi).
Conclusion
CMT is the first manifestation of MEN2A. As shown in this case the age of prophylactic thyroidectomy is of decisive importance to the prognosis. Tumour somatostatin receptors heterogeneity may be responsible for different responses to radionuclides. The treatment of metastatic disease is challenging due to the poor response to systemic therapy and/or radiotherapy.

DOI: 10.1530/endoabs.37.EP1303

EP1304

Coexistent medullary and papillary thyroid carcinomas

Betül Ekiz-Bilir[1], Neslihan Soysal-Atile[1], Zehra Dagli[2] & Ufuk Coskunkan[3]
[1]Endocrinology Department, Tekirdag State Hospital, Tekirdag, Turkey; [2]Pathology Department, Tekirdag State Hospital, Tekirdag, Turkey; [3]General Surgery Department, Namik Kemal University, Tekirdag, Turkey.

Papillary thyroid cancer (PTC) is the most frequent thyroid tumour. Medullary thyroid cancer (MTC) however, is very rare. We report a case of coexistent

medullary and papillary carcinomas in two different foci in a patient with family history of TPC in a first-degree relative.
Case
A 65-year-old female was examined for multinodular goiter (MNG). She had a family history of thyroid papillary carcinoma in her elder sister. Free T_4, free T_3, and TSH levels were within normal limits. Neck ultrasound (US) displayed solid, hypo-echoic nodules >3 cm at the both lobes of the thyroid gland. The results of fine-needle aspiration cytology (FNAC) of the both nodules were benign. Patient preferred surgery because of the nodule size and positive family history. Histopathology results revealed MTC which is 4 mm in diameter in the right lobe and PTC follicular variant 12 mm in diameter in the left lobe. Postoperative calcitonin was 56 pg/ml and CEA was in normal limits. Completion thyroidectomy and lymph node dissection also performed. No residue was detected by post-operative neck US. Neck and chest CT and liver MRI which were performed for MTC metastasis were all negatives. RET protooncogen mutation was negative unless $BRAF^{V600E}$ mutation was positive. Patient's younger sister was also examined for MNG. Thyroid US displayed solid, hypoechoic nodules >2 cm in both lobes. FNAC of nodules were reported as suspicious for PTC. Patient underwent total thyroidectomy and central lymph node dissection and diagnosed as PTC on both lobes.
Discussion
FNAC is the most accurate method for evaluating thyroid nodules. False negative rate of FNAC is about 5%, so malignancy risk of benign results should be kept in mind especially with a positive family history of thyroid carcinoma in a first-degree relative. We presented a coincidental coexistence of MTC and PTC case to point to this risk.

DOI: 10.1530/endoabs.37.EP1304

EP1305

Virilisation due to a Leydig cell tumour of the ovary: diagnostic and therapeutic challenges

Ruxandra Dobrescu[2], Cristian Poalelungi[1], Iuliana Ceausu[1], Dan Hortopan[2] & Corin Badiu[1,2]
[1]'Carol Davila' University of Medicine and Pharmacy, Bucharest, Romania; [2]'C.I.Parhon' National Institute of Endocrinology, Bucharest, Romania.

Introduction
Severe hirsutism and virilisation, especially if occurring later in life and with rapid onset, should prompt the search for rare but potentially threatening causes such as an androgen secreting ovarian or adrenal tumour.
We present the case of a 47-year-old woman referred to our clinic with obesity, severe hirsutism, alopecia, acne, and deepening of the voice that appeared insidiously 2 years ago, along with amenorrhoea which she interpreted as menopause. Laboratory testing revealed polycythemia, impaired glucose tolerance, normal thyroid, IGF1, 17OH- progesterone, baseline ACTH, cortisol, and DHEAS levels with adequate suppression of cortisol after low dose ($2\times$ 2 mg). Dexamethasone suppression testing (LDDST) excluding an adrenal hypersecretion. She had severe hyperandrogenism – total testosterone $=$ 6.38 ng/ml which increased paradoxically after LDDST (7.57 ng/ml) and normal gonadotropins and oestrogens (LH $=2.63$ mUI/ml, FSH $=5.59$ mUI/ml, and oestrogen $=86$ pg/ml) reflecting either androgen induced amenorrhea in premenopause, or testosterone mediated gonadotropin suppression after menopause. CT scans of the abdomen and pelvis and the ultrasound evaluation of the uterus and ovaries showed normal morphology – raising suspicion of ovarian hyperthecosis. The patient initially postponed surgery, so a short trial of GnRH agonist was attempted (triptorelin 0.1 mg s.c./month) with a small decrease in testosterone to 5.65 ng/ml after 1 month, further proving its ovarian origin. A repeat ultrasound showed a 1.94/1.65 cm mass in the right ovary, suggesting an androgen-secreting ovarian tumour. The patient underwent bilateral oophorectomy and total hysterectomy and the pathology report confirmed a benign Leydig cell tumour of the ovary. Testosterone levels normalized immediately post-surgery (0.30 ng/ml) and after 6 months the hirsutism and alopecia were significantly improved, haemoglobin levels normalized, but the obesity persisted and diabetes mellitus was diagnosed.
Conclusion
Although, typically large, Sertoli–stromal ovarian tumours can occasionally be small enough to avoid detection even by high-resolution imaging; in the presence of virilisation the differential diagnosis includes ovarian hyperthecosis. In either situation bilateral oophorectomy is recommended after the end of childbearing years.

DOI: 10.1530/endoabs.37.EP1305

EP1306

Takotsubo cardiomyopathy associated with levothyroxine over-replacement

Ana Margarida Balsa[1], Raquel Ferreira[2], Rosa Dantas[1] & Joana Guimarães[1]
[1]Serviço de Endocrinologia, Diabetes e Nutrição do Centro Hospitalar do Baixo Vouga, Aveiro, Portugal; [2]Serviço de Cardiologia do Centro Hospitalar do Baixo Vouga, Aveiro, Portugal.

Background
Takotsubo cardiomyopathy (TC) is characterised by acute, transient left ventricular apical ballooning precipitated by emotional or physiologically stressful stimuli and has been previously associated with Graves' disease based on few clinical reports. More recently, the association with exogenous thyrotoxicosis and radioiodine-induced thyroiditis has also been described. Iatrogenic hyperthyroidism on patients under levothyroxine replacement therapy for hypothyroidism had never been reported as a cause of TC. The authors describe two female patients with TC associated with levothyroxine over-replacement.
Case description
A 74- and 48-year-old female patient, medicated with levothyroxine (2.27 and 1.85 μg/kg respectively) for autoimmune thyroiditis was both admitted on our emergency room with precordial pain. The first had an ECG with ST-segment elevation in the anterior precordial leads, and the latter had sinus tachycardia with deep T-wave inversion and QT interval prolongation. Further investigation revealed a mild elevation of cardiac biomarker levels, severe apical hypokinesis but no significant coronary lesions on catheterisation. The suppressed TSH levels were only demonstrated on the cardiac intensive care unit: 0.21 and 0.07 mIU/l (0.35–5.50) respectively. Both patients showed improvement of the apical hypokinesis on the discharge echocardiogram and normalisation of cardiac biomarker levels. Levothyroxine dose was reduced.
Commentary
This case report emphasizes the importance of correct dose adjustment on patients under levothyroxine replacement therapy and stresses that TSH should be determined in patients presenting with acute coronary syndrome and typical finding of TC.

DOI: 10.1530/endoabs.37.EP1306

EP1307

Conversion of autoimmune hypothyroidism to hyperthyroidism with thyroid eye disease

Maura Moriarty, Edouard Mills, Hsiu L Yap & Arif Hamda
Department of Endocrinology, Watford General Hospital, Watford, UK.

We report the case of a 41-year-old lady who developed severe thyroid eye disease on a background of long standing hypothyroidism. She had been diagnosed with autoimmune hypothyroidism 15 years previously with positive TPO antibodies. She had been successfully maintained on levothyroxine replacement since then. She presented with a four year history of progressive eye swelling, gritty eyes and diplopia. On examination she was found to have active thyroid eye disease with restriction of extra-ocular movement, proptosis and diplopia. In addition her thyroid function tests showed suppressed TSH indicating probable over replacement with thyroid hormone. Her levothyroxine dose was weaned and eventually discontinued. She proceeded to have a course of steroids with some reduction in her visual symptoms. Unfortunately, she developed significant symptoms of thyrotoxicosis off thyroid replacement. Thyroid uptake scan showed generally increased uptake in the right lobe with no evidence of a nodule on ultrasound. TSH receptor antibodies at this time were strongly positive. Unfortunately her eye disease relapsed and she required orbital decompression surgery to which she had a good functional and cosmetic response. Thyroid function normalised rapidly on carbimazole and she was able to discontinue treatment after nine months. Following a period where she was biochemically euthyroid TSH levels have begun to rise again. We postulate that this lady had TSH receptor antibodies which were variably stimulating or blocking the TSH receptor as an underlying cause for her presentation. This case highlights the need to consider thyroid eye disease in a patient presenting with visual symptoms and a history of autoimmune thyroid disease. It also illustrates the need to have a high index of suspicion for possible conversion of

hypothyroidism to hyperthyroidism in a patient rather than attributing the biochemical abnormality solely to over replacement with thyroid hormone.

DOI: 10.1530/endoabs.37.EP1307

EP1308

Pulmonary neuroendocrine tumour presenting with thyroid gland metastasis: a case report

Cristina Corina Pop Radu
University of Medicine and Pharmacy, Tirgu Mures, Romania.

Introduction
Neuroendocrine tumours (NET) represent ~20% of all primary neoplasms of the lung. Histologic confirmation is important for treatment and prognosis determination. NET are classified according to four subtypes in the lung: typical carcinoid tumour (TC), atypical carcinoid tumour (AC), small cell carcinoma (SCC), and large cell neuroendocrine carcinoma (LCNEC). TC is low-grade, AC is intermediate-grade, and SCC and LCNEC are high-grade malignancies.
Case report
A 57-year-old woman, affected by a cervical anterior tumour and a proliferative tissue below the glottis was referred to our Endocrinology Department from ENT service for a second opinion. An ultrasound scan of the neck showed a polynodular goitre with bilaterally lymph nodes enlargement with suspicious malignancy characters. She had undergone surgery for the cervical anterior mass and for the laryngeal biopsy. Histopathological examination results were consistent with a SCC; neoplastic cells showed immunoreactivity to synaptophysin, neuron specific enolase, and chromogranin. The serum levels of serotonin, cromogranin A, calcitonin, carcinoembryonic antigen, ACTH, PTH, TSH, and FT_4 were normal. Fine-needle aspiration biopsy of her left thyroid lobe nodule was performed and the cytopathological exam was compatible with a neuroendocrine tumour metastasis. Thoracic and abdominal computed tomography was normal at that moment. Chest CT revealed the primary pulmonary tumour at 6 months after presentation. The therapeutic option for advanced or metastatic NETs is mainly palliation of symptoms; options need to be individualised and, therefore, rely on the knowledge of multidisciplinary teams.

DOI: 10.1530/endoabs.37.EP1308

EP1309

Graves' disease and pregnancy

Imane Leghbir, Samia Ould Kablia & Meriem Bensalah
Central Hospital of the Army, Algiers, Algeria.

Introduction
Pregnancy for women with Graves' disease is at risk for the mother and the newborn. In fact neonatal hyperthyroidism is uncommon, often transient in the context of maternal Graves' disease (1% of children). Immediate treatment is essential for a good prognosis, prenatal treatment improves foetal and neonatal development.
Case report
We report the case of a patient, known for Graves' disease since 2006, treated initially with carbimazole for 18 months.She was in remission for 2 years, but in December 2013 as she relapse, she was treated by radio-iodine (one month before conception). She gave birth to a premature 31 SA, in 21 August 2014 with subclinical hyperthyroidism (TSH: 0.07 UI/ml and FT_4: 7.09 pg/ml). After 15 days the new born present an overt hyperthyroidism (TSH: 0.01 UI/ml and FT_4: 23.5 pg/ml) with TSI: 6.89 UI/l. The baby receives carbimazole for 2 months and became euthyroid.
Conclusion
Neonatal hyperthyroidism should be screened in all newborn from mother with Graves' disease treated by radical treatment (radio-iodine or thyroidectomy) because TSI freely cross the placental barrier and thus stimulate the thyroid of the newborn. Prognosis of neonatal hyperthyroidism mediated by anti maternal body is quite good as they disappear in 4–12 weeks after birth.

DOI: 10.1530/endoabs.37.EP1309

EP1310

The Ehlers-Danlos syndrome and metastatic medullary thyroid carcinoma: a case report

Lina Zabuliene[1,2], Airida Audrone Bagdziuniene[3], Birute Burnyte[4], Ramunas Janavicius[5], Jurgita Urboniene[6] & Algirdas Utkus[4]
[1]Clinics of Rheumatology, Traumatology–Orthopaedics and Reconstructive Surgery, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [2]Antakalnio Out-Patient Clinic, Vilnius, Lithuania; [3]Centre of Endocrinology, Vilnius University Hospital Santariskiu Klinikos, Vilnius, Lithuania; [4]Department of Human and Medical Genetics, Faculty of Medicine, Vilnius, Lithuania; [5]Department of Molecular and Regenerative Medicine, Hematology, Oncology and Transfusion Medicine Center, Vilnius University Hospital Santariskiu Clinics, Vilnius, Lithuania; [6]Infectious Diseases and Tuberculosis Hospital, Vilnius University Hospital Santariskiu Klinikos, Vilnius, Lithuania.

Introduction
The Ehlers-Danlos syndrome, classic type is a connective tissue disorder, characterized by skin hyperextensibility, abnormal wound healing, and joint hypermobility, due to *COL5A1* or *COL5A2* genes mutations. Multiple endocrine neoplasia, type 2A (MEN2A) is a syndrome defined by medullary carcinoma, phaeochromocytoma, hyperparathyroidism, and occasionally cutaneous lichen amyloidosis, because of mutations in *RET* proto-oncogene. *COL5A* and *RET* genes mutations are linked to conditions affecting the human integumentary system.
Case report
A 18-year-old Caucasian female was consulted by endocrinologist in February 2014. Her psychomotor development was normal. Since childhood she was very flexible. At age 12 she had hip luxation and underwent internal fixation with screws. Deformities of pelvis and lumbar spine, knee valgus deformity occurred. At 15 years juvenile epiphysiolisis was diagnosed. She underwent left knee osteosynthesis followed by peroneal and tibial nerves damage. In 2012 small thyroid nodule, subclinical hypothyreosis was diagnosed; 25 mg of levothyroxine were prescribed. In 2014 medullary carcinoma (size 0.4 mm) was diagnosed. Thyroidectomy and neck lymphnodectomy was performed. She received radiotherapy course. 2.5 weeks after surgery calcitonin level was 1557.2 ng/l (0.5–7.8). She has been taking levothyroxine 125 mg/day. Her mother has MEN2A and underwent surgery for parathyroid adenoma. Father has multinodular goitre. On examination: height 184 cm, long face, long palms and fingers, joints' hypermobility, scoliosis, widened atrophic scars, atrophic striae at the back, hyperelasticity of face and elbows skin, piezogenic papules. Abdominal ultrasound and CT: no pathological changes. Left shoulder CT: sclerotic proximal growth line of left humerus. Body CT: multiple lymphnodes, lungs, pelvis bones, and vertebrae metastases. Bone scan: active head, humerus, pelvis focuses. Genetics'. Ehlers-Danlos syndrome; *RET* gene mutation at 13th egzone (*Y791F* mutation), causing MEN2A syndrome.
Conclusions
If complicated growth and atypical phenotype is obvious, genetics' consultation is desirable. Coexistent thyroid pathology might be inherited too.

DOI: 10.1530/endoabs.37.EP1310

EP1311

Takotsubo cardiomyopathy in a young woman with severe adrenal insufficiency and hypothyroidism

Aleksandra Kruszynska[1], Jadwiga Slowinska-Srzednicka[1] & Agata Popielarz-Grygalewicz[2,3]
[1]Department of Endocrinology, The Medical Centre of Postgraduate Education, Warsaw, Poland; [2]Department of Cardiology, Bielanski Hospital, Warsaw, Poland; [3]Department of Cardiology, Faculty of Physiotherapy, Warsaw Medical University, Warsaw, Poland.

Introduction
Acute cardiac insufficiency induced by stress (Takotsubo cardiomyopathy (TTC)) is a reversible cardiomyopathy induced by severe emotional stress or severe clinical conditions. It is characterised by transient left ventricular systolic dysfunction and electrocardiographic changes. This cardiomyopathy has been described in some severe neurological conditions and in patients with pheochromocytoma. To date, some cases of this cardiomyopathy have been described in patients with hyponatremia due to isolated secondary adrenal insufficiency or in a patient with both hypothyroidism and adrenal insufficiency. TTC has been known to be more prevalent in women (the role of sex and hormones is not yet well defined).
Case report
We present a case of a 43-year-old woman with hypopituitarism, probably due to autoimmune hypophysitis with secondary hypothyroidism, secondary adrenal

insufficiency, and hypogonadism as well as with primary hypothyroidism due to Hashimoto's thyroiditis. The patient was treated for primary hypothyroidism, but her general condition suggested adrenal insufficiency. On admission, her plasma cortisol was 0 μg/dl, so she was treated immediately with hydrocortisone. As a routine examination, echocardiography was performed revealing ampulla cardiomyopathy. Electrocardiography showed T wave inversion in almost all leads. Two weeks after treatment with hydrocortisone and thyroxine, an echocardiographic examination showed recovered left ventricular wall motion and improvement in the ejection fraction and electrocardiography was normal. This is, to our knowledge, the first report of TTC due to hypothyroidism and adrenal insufficiency with no hyponatremia, no evident hypoglycemia and no evident catecholamine overproduction.

Conclusions

Adrenocortical failure is considered to be one of the triggering factors for ampulla cardiomyopathy. All patients with severe adrenal insufficiency should be screened for cardiomyopathy and first-line treatment in these cases consists of proper steroid substitution and careful monitoring of cardiac function.

DOI: 10.1530/endoabs.37.EP1311

EP1312

A rare association: primary hyperparathyroidism and thyroid papillary carcinoma: case report

George-Sebastian Zmău[1], Cristina Preda[1], Cipriana Stefanescu[2], Radu Danila[3], Delia Ciobanu[4], Iulia Crumpei[1], Alina Daniela Belceanu[1], Adina Manolachie[1] & Carmen Vulpoi[1]
[1]Department of Endocrinology, UMF 'Gr. T. Popa' Iasi, Iasi, Romania; [2]Department of Nuclear Medicine, UMF 'Gr. T. Popa' Iasi, Iasi, Romania; [3]Department of General Surgery, UMF 'Gr. T. Popa' Iasi, Iasi, Romania; [4]Department of Morphopathology, UMF 'Gr. T. Popa' Iasi, Iasi, Romania.

Introduction

Although, the relationship between pathological process of the parathyroid and thyroid is common, concurrence of primary hyperparathyroidism (pHPT) and papillary thyroid carcinoma (PTC) is extremely rare, probably because, unlike with medullary thyroid cancer, they have not a common embryologic origin. We present a case with this uncommon association.

Case report

A 67-year-old woman with multinodular goitre was addressed in endocrinology for persistent hypercalcaemia 11.24 mg/dl and hypophosphatemia 2.4 mg/dl. High PTH value (119 pg/ml (normal range 10–69 pg/ml) confirmed primary hyperparathyroidism. The neck ultrasound revealed a potential 0.4 ml parathyroid adenoma at the superior pole of the right thyroid lobe and a 6 ml nodular conglomerate with central necrosis in the left thyroid lobe. The ^{99m}Tc-sestamibi parathyroid scintigraphy revealed an area with increased uptake in the projection aria of the nodule described at ultrasonography. Owing to the nodular aspect of the contralateral lobe total thyroidectomy was performed and the histological examination diagnosed right superior parathyroid adenomatous hyperplasia and multicenter invasive papillary carcinoma in the left thyroid lobe with (pT3Nx-G1). Hyperparathyroidism was cured, with normal PTH and phosphocalcic parameters. For the invasice PTC radioiodine therapy was performed with complete remission from – cifra! – ani. She is no more on suppressive L-T_4, having low normal TSH and absent thyroglobulin.

Conclusion

Our case illustrates an extremely rare synchronous association of primary hyperparathyroidismn with thyroid carcinomas (with an incidence roughly estimated at 0.0023/100 000 person-years). In spite of its rarity, this coexistence of pHPT and PTC maybe not a random but a possible new pathology. The concurrence of both pathological processes can make the patient management complicated, because unrecognised thyroid cancer diagnosed at the histological examination implies surgical re-intervention.

DOI: 10.1530/endoabs.37.EP1312

EP1313

Fainting matters: a case of an autoimmune polyglandular syndrome with an atypical involvement of the parathyroid gland

Ieva Ruza[1,2], Sabine Upmale[2], Justine Malina[2] & Inta Leitane[1]
[1]Riga Eastern Clinical University Hospital, Riga, Latvia; [2]Riga Stradins University, Riga, Latvia.

Introduction

The autoimmune polyglandular syndrome (APS) is characterised by the coexistence of at least two glandular autoimmune mediated diseases. We report a combination of an autoimmune thyroid disease, Addison's disease and an atypical involvement of the parathyroid gland.

Case report

A 73-year-old white woman was admitted to our clinic for evaluation due to recurrent syncopes during last 3 years, along with vertigo, cold sweats, and general fatigue, associated with prolonged standing. Three months ago she was diagnosed with chronic autoimmune thyroiditis and primary hypothyroidism, as well as a parathyroid gland adenoma. Head CT scan revealed basal ganglia calcinosis. The patient had lost 15 kg within the past year, during investigation orthostatic hypotensia was detected, no skin colour changes. Biochemical tests revealed low aldosterone, renin, calcium, free T_4 and mildly elevated creatinine serum levels. TSH was elevated, ACTH was high normal. She had low cortisol in 24 h urine and also in serum after insulin stress test. PTH level was normal, but coexisting hypocalcaemia and parathyroid gland adenoma must be taken into consideration. Antibody screen (ANA, thyroid peroxidase, and tranglutaminase) was negative. No substantial changes in other tests. No data on diabetes mellitus or malignancy was found. Diagnosis of primary adrenal insufficiency with glucocorticoid and mineralocorticoid deficiency, chronic autoimmune thyroiditis with primary hypothyroidism, hypocalcaemia, calcinosis of basal ganglia (possible Fahr's syndrome), parathyroid gland adenoma, secondary osteoporosis due to malabsorption, chronic kidney disease was made. Based on these findings we suggest the final diagnosis of type 2 autoimmune polyglandular syndrome. Treatment was continued with L-thyroxine and oral calcium, started with alphacalcidol, hydrocortisone, fludrocortisone. A substantial improvement of symptoms was seen in a control visit after 3 months.

Conclusion

We would like to stress the importance of investigation for autoimmune glandular diseases and electrolyte level in case of unexplained syncope.

DOI: 10.1530/endoabs.37.EP1313

EP1314

Subacute thyroiditis due to seasonal influenza vaccination

Fatma Aybala Altay[1], Galip Güz[2] & Mustafa Altay[3]
[1]Department of Infectious Disease and Microbiology, Ankara Dişkapi Yildirim Beyazid Education and Research Hospital, Ankara, Turkey; [2]Department of Nephrology, Medical Faculty, Gazi University, Ankara, Turkey; [3]Department of Endocrinology and Metabolism, Keçiören Education and Research Hospital, Ankara, Turkey.

Introduction

Subacute thyroiditis due to vaccination is reported in only a few case reports. A peritoneal dialysis patient who experienced a repeating attack after a vaccination for influenzae while she was being followed and treated successfully for subacute thyroiditis is presented.

Case

A 28-year-old female patient who has been applying dialysis for nine years was seen in policlinic telling about upper respiratory tract infection 2 months ago and pain at her thyroid lodge for 3 weeks. Her thyroid was palpable and tender. She was diagnosed as subacute thyroiditis with high levels of ESR, CRP, TSH, anti-TG, TPO, and consistent ultrasonography findings. She was begun ibubrofen at 1800 mg/day in three divided doses after consulting with nephrology. She had recovered totally a week after and begun to follow up with levotyroxine 75 μg/day. She applied to hospital 3 months later with fatigue, fever, sore throat, dyspnea, pain, and swelling at her thyroid lodge again. USG showed a larger thyroid. ESR, CRP, anti-TG, and anti-TPO were much more higher. It was learnt that she had been vaccinated for influenza 3 weeks ago and began to suffer from gribal symptoms at the third day and pain and swelling of thyroid at the second week of vaccination. Her thyroid scintigraphy showed heterogenous and lower activity and her thyroid biopsy resulted as consistent with subacute thyroiditis. So the patient was diagnosed as subacute thyroiditis and ibubrofen was begun besides raising levothyroxine dose to 100 μg/day. Methyl prednisolone of 40 mg/day was added because there was no symptomatic improvement at the third day. The symptoms regressed after steroid in three days and recovered totally at the end of the first week. Steroid was stopped by gradually declining at the third week.

Discussion

Influenza like symptoms is known to develop after vaccination. This case is showing a rare condition due to vaccination to cause a subacute thyroiditis just like the virus can make.

DOI: 10.1530/endoabs.37.EP1314

EP1315

Testicular pain as an initial complaint in patient with classic form of Klinefelter's syndrome: a case report

Svetlana Jelic[1,2], Aleksandra Jevic-Ivanovic[1] & Stanislava Zivkovic[1]
[1]Clinical Hospital Center Bezanijska Kosa, Belgrade, Serbia; [2]School of Medicine, University of Belgrade, Belgrade, Serbia.

Background
In spite of being the most frequent genetic form of male hypogonadism, Klinefelter's syndrome is not so rarely undiagnosed until adulthood. As the severity of manifestations in Klinefelter's syndrome is proportional to the number of additional X chromosomes, they seem less severe and aparent in its classic form, with a 47,XXY karyotype than in cases of this syndrome with mosaicism and other variants.
Case report
A 25-year-old male was refered for endocrinological evaluation by urologist because of the chronic testicular pain preventing effective testosterone replacement of already proven hypogonadism. The physical examination revealed normal height, long limbs, muscular weakness, and reduced or completely absent hair in the androgen-dependent regions. There are clinical signs of testicular dysgenesis. Hormone measurements were as follows: ACTH, 37.74 pg/ml; cortisol, 505.9 nmol/l; TSH, 1.81 μIU/ml; fT_4, 15.15 pmol/l; LH, 31.78 mIU/ml; FSH, 53.39 mIU/ml; free testosterone, 5.0 pg/ml; PRL, 519.9 mIU/l; and vitamin D, 21.25 ng/ml. MRI demonstrated a profound arachnoid recessus hustling the pituitary toward the dorsum of the sella turcica. Densitometry showed osteopenia with the L1–L4 *T*-score of −2.7 and the hip *T*-score of −2.1. Assessment of the karyotype point out to the classic, 47,XXY form of Klinefelter's syndrome and testosterone replacement was initiated with the close follow-up of its effects.
Conclusions
The case presented demonstrates a classical form of the Klinefelter's syndrome with not so classical presentation of testicular pain which halted the correction of proven androgen deficiency. Coexistant empty sella with hyperpolactinaemia demand further periodical reassessment.

DOI: 10.1530/endoabs.37.EP1315

EP1316

Ectopic ACTH syndrome: diagnostic and therapeutic challenge

Katarzyna Piatek, Malgorzata Kaluzna, Katarzyna Ziemnicka & Marek Ruchala
Department of Endocrinology, Metabolic Diseases and Internal Medicine, Poznan University of Medical Science, Poznan, Poland.

Introduction
Rapid deterioration of health condition in patient with diagnosed neoplastic disease, especially metastatic one, requires consideration of cancer progression. However other rare severe complications can occur. In 0.6–0.7% patients with medullary thyroid cancer (MTC) the ectopic ACTH syndrome (EAS) is observed. Hereby, we present a case EAS in patient suffered from MTC.
Case report
A 37-year-old man was admitted to the Department of Internal Medicine in serious clinical condition with general fatigue and chest pain. Myocardial infarction has been excluded. Patient's past medical history was remarkable for MTC with numerous reoperations. Routine laboratory test showed *de novo* diabetes mellitus. Calcitonin serum level was 499.53 pg/ml (*n*: 0–10 pg/ml). Additional tests revealed severe hypercortisolaemia (cortisol level 2100 nmol/l; *n*: 0700–1000 h: 171–536 nmol/l). The patient was referred to the Department of Endocrinology for further diagnostics and treatment. ACTH level was 329.0 pg/ml ($n<60.0$). There was no suppression of cortisol secretion after 1 mg of dexamethasone. Magnetic resonance imaging (MRI) of the pituitary gland showed no signs of macro or microadenoma. Computer tomography (CT) of the chest revealed metastasis to the mediastinum lymph nodes. The adrenal glands in CT were normal size and shape. The EAS was diagnosed. Owing to the rapid deterioration of general condition despite of ketoconazole treatment, bilateral adrenalectomy was performed. The patient in severe condition was transferred to the Intensive Care Unit. Four reoperations were conducted due to the: internal bleeding, megacolon toxicum, faecal peritonitis and eventration. On the 41th day after first surgery the patient died due to sepsis.
Conclusions
The EAS is a rare condition in patients with MTC, but our patient's history should serve as a warning to actively seek of EAS in case of metastatic disease, especially in rapid health deterioration.

DOI: 10.1530/endoabs.37.EP1316

EP1317

Stress cardiomyopathy following radioactive iodine therapy: a case report

Anastasia Dimakopoulou, Karunakaran Vithian, David Ganon & Alan Harkness
Colchester Hospital, Essex, UK.

A 55-year-old female presented to the Endocrine Clinic with Graves' disease which was treated with carbimazole for 18 months. Her initial symptoms were facial sweating and dry lips on background of a multinodular goitre confirmed on thyroid ultrasound. TSH was <0.01 mU/l, free T_4 was 42.2, and free T_3 18 pmol/l. Thyrotoxicosis recurred in an attempt to taper down the dose of carbimazole and a decision was made to proceed with radioactive iodine treatment. Four days after radioiodine administration, our patient presented to the Emergency Department with chest tightness and dyspnoea. TSH was undetectable and free T_4 was 77.7 pmol/l. ECG was consistent with sinus tachycardia and borderline ST elevation in II/III leads. Troponin was elevated at 438 ng/l. Our patient was transferred to the local cardiothoracic center, where echocardiography revealed left ventricular ejection fraction of 30–35%. Coronary angiography showed no obstructive coronary disease. This is a case of stress cardiomyopathy which developed in the context of radiation thyroiditis. Complete recovery was achieved after treatment with propylthiouracil, ramipril, carvedilol, and a course of steroids. Six weeks later left ventricular function was noted to be normal on echocardiography and hypothyroidism was evident on thyroid function testing. This the second case of stress cardiomyopathy following radioactive iodine therapy reported in the literature, to the best of our knowledge. Left ventricular dysfunction is reversible in stress cardiomyopathy although patients can present quite unwell. High index of suspicion along with early thyroid testing may lead to successful treatment without unnecessary diagnostic investigations.

DOI: 10.1530/endoabs.37.EP1317

EP1318

Is thymectomy a solution for myasthenia gravis associated with autoimmune thyroid diseases?

Ioana Vasiliu, Ioana Bodescu, Cipriana Stefanescu, Delia-Gabriela Ciobanu, Lidia Ionescu, Ionela Lacramioara Serban & Carmen Vulpoi
University of Medicine and Pharmacy, Iasi, Romania.

Myasthenia gravis (MG) and autoimmune thyroid diseases (AITD) may coexist and influence one another clinical expression. The opportunity of thymectomy in this association is controversial, since not all the studies have proven its efficacy. We report eight patients (one man and seven women) diagnosed with AITD (Graves' disease (GD) – five cases, Hashimoto's thyroiditis (HT) – three cases) and MG. The AITD diagnosis preceded (two cases), followed (three cases) or occurred simultaneously (three cases) with MG. In most cases thyroid disease had a good evolution with medical treatment. Four cases underwent thyroidectomy: one for intolerance to antithyroid drugs, two severe relapse of GD, and one for large nodular goitre with compression symptoms. All patients had imagistic investigation of thymus area: CT, scintigraphy with 99Tc-tetrofosmin. Treatment was started with anticholinesterase drugs (ACD). Thymectomy was performed in six cases either for tumoural aspect on imagery or inefficacy of ACD. Surgery was performed, on demand, in one case with normal imagery and stable evolution. Thymectomy in this particular case did not modify the evolution. Three cases with evolution of MG for <1 year, had an improvement of the myasthenia after thymectomy. One of them, the man, who associated three autoimmune diseases, had also an improvement of the HT. One case, with a 4 years evolution of MG and HT, had no improvement after thymus resection. Last case had an unfortunate evolution, with postsurgical death. The two cases, not operated, had a good evolution of AITD followed by an amelioration of the MG symptoms. The association of MG and AITD may influence one-another evolution. Generally, the amelioration of the thyroid dysfunction induces an improvement of MG. Thymectomy may improve the evolution of MG if performed in the first year of diagnostic. Longer evolution leads to irreversible alterations; therefore the myasthenic symptoms cannot be improved.

DOI: 10.1530/endoabs.37.EP1318

EP1319

Polydipsia and polyuria, differential diagnosis in pregnancy

Esther Delgado[1] & Cristina Tejera[2]
[1]University Hospital of Badajoz, Badajoz, Extremadura, Spain; [2]University Hospital of Ferrol, Ferrol, Galicia, Spain.

Introduction
Gestational diabetes insipidus (GDI) is a rare endocrinopathy whose incidence is around four cases per 100 000 pregnancies. It is a potentially life threatening state. We present a case of a 39 year old with GDI.
Case report
A previously healthy 39-year-old woman in her 37th week of gestation presented dry oral mucosa with polydipsia and polyuria of 8 l over 24 h for approximately 2 month. The prenatal course of the pregnancy was uncomplicated until 35 weeks. Medical history was an appendectomy and she had on treatment of female infertility with *in vitro* fertilisation. On admission, well general condition, blood pressure 105/60 mmHg and 75 beats/min and saturating 99% on ambient air. The physical and gynaecological examinations were unremarkable. Laboratory studies revealed: serum sodium of 140 mEq/l, potassium 4.3 mEq/l, chloride 108 mEq/l, glucose 79 mg/dl, creatinine 0.7 mg/dl, calcium 8.2 mEq/l, total protein 5.9 gm/dl, FA 142 units/l, AST 584 units/l, and ALT 613 units/l. The serum osmolality was 294 mOsm/kg; and urine osmolality was inappropriately low. Other laboratory datas were normal. Water deprivation test and treatment with DDAVP confirmed diagnosis. Twelve hours after admission, she had a female infant by spontaneous vaginal delivery with APGAR scores were 8, 10 at 5, and 10 min, respectively. Laboratory evaluation of the infant was normal. Post-delivery, polydypsia and polyuria were resolved. GDI was resolved after delivery.
Conclusions
The diagnosis of gestational DI is often not diagnosed because polyuria in pregnancy is generally considered normal. We should suspect in patients with typical symptoms or with risk factor because sometimes, GDI can be associated with serious pathology like fatty liver of pregnancy and pre-eclampsia that might lead to foetal demise.

DOI: 10.1530/endoabs.37.EP1319

EP1320

Hyperprolactinemia and Leydig cell tumor

Ana Margarida Monteiro, Marta Alves & Olinda Marques
Department of Endocrinology – Hospital de Braga, Braga, Portugal.

Introduction
Leydig cell tumors are the most common testicular sex cord stromal tumors. The most frequent clinical presentation is a testicular mass. However, they can present with endocrine manifestations, and gynecomastia is the most common presentation. Hyperprolactinemia can cause hypogonadotropic hypogonadism, and in males, is also a cause of gynecomastia.
Clinical case
A 24-years-old male was referred to our Endocrinology Department due to hyperprolactinemia and increasing bilateral breast volume with a year of evolution, without galactorrhoea, libido changes or erectile dysfunction. He had irrelevant medical past history, without medication, smoking, alcohol or illicit drug use. On physical examination, bilateral painful gynecomastia, without palpable nodules, skin changes or nipple retraction or galactorrhea. Testes were present, with no palpable nodules. Laboratory exams revealed normal testosterone and FSH, slightly low LH (1.43 mIU/ml (1.5–9.3)), high estradiol (206.02 pmol/l (<146.1)) (although normal in its first evaluation) and high prolactin levels (27.08/35.49/30.30 ng/ml (2.1–17.7)). TSH was normal and testicular tumour markers were normal. Breast ultrasound showed increased bilateral mammary glands, compatible with gynecomastia. The pituitary MRI showed an area of low uptake which could correspond to a microadenoma. He started bromocriptine 2.5 mg/day. In the scrotal ultrasound an isoechogenic nodule with 12 mm in the right testicle was observed. He was referred to the urology consultation. Scrotal RM confirmed the nodule in the right testicle. He was submitted to right partial orchiectomy guided by ultrasound, and histological examination revealed a Leydig cell tumor. He was oriented to plastic surgery to bilateral mastectomy. After surgery, we stopped bromocriptine use and pituitary MRI was normal. Currently, he has normal prolactin levels.
Discussion
Prolactinomas and Leydig cells tumors are possible causes of gynecomastia and hyperprolactinemia (in the last because of hyperestrogenism) making it sometimes a challenge the evaluation of prolactin levels in this context.

DOI: 10.1530/endoabs.37.EP1320

EP1321

Can pericardial effusion be a manifestation of Graves' disease? An unusual case

George Besis[1], Nikolaos Kyriakakis[2] & Lakdasa D Premawardhana[3]
[1]Department of Cardiology, University Hospital of Wales, Cardiff, UK; [2]Leeds Centre for Diabetes and Endocrinology, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, UK; [3]Section of Endocrinology, Department of Medicine, Ysbyty Ystrad Fawr, Hengoed, UK.

Introduction
Graves' disease (GD) is associated with a number of cardiovascular complications, including rhythm disturbances, mitral valve prolapse, pulmonary hypertension and heart failure. Pericardial effusion in the context of GD has only been reported in a small number of cases.
Case
A 59-year-old gentleman presented with a 3-day history of dyspnoea and pleuritic chest pain. He had a previous history of GD 8 months ago, pulmonary embolism (PE), asthma, hypertension, obesity and was established on warfarin, following a second episode of PE, 4 weeks prior to this clinical event. Clinical examination revealed tachypnoea, tachycardia, raised JVP and bibasal crackles. Echocardiography showed a 2.9 cm pericardial effusion, compromising the right ventricular filling. 10 days prior to this admission, a previously echocardiogram had shown a smaller size pericardial effusion. TFTs showed suppressed TSH, elevated free T_4 at 34.7 pmol/l (reference range 9.2–21 pmol/l) and positive TSH receptor antibodies, compatible with relapsed GD. Other laboratory investigations showed acute kidney injury (eGFR 38 ml/min per 1.73 m^2) and elevated INR at 17.2, which was pharmacologically reversed. Interestingly, 10 days prior to admission the patient had normal renal function. Analysis of the pericardial fluid showed inflammatory cells. Microbiology and cytology investigations were unremarkable. A full body CT scan did not show evidence of neoplastic process. The patient was stabilised following pericardiocentesis and was commenced on Carbimazole 40 mg daily.
Conclusions
This is an unusual presentation of GD. The patient was investigated extensively, but no alternative cause for pericardial effusion was found. The presence of inflammatory cells in the fluid, suggests an inflammatory pericarditis. GD could have also been implicated in the pathogenesis of the patient's recent PE, given the thrombogenic tendency that hyperthyroidism is associated with. We therefore recommend that TFTs should be undertaken in patients presenting with unexplained pericardial effusion and equally patients with GD presenting with dyspnoea should undergo echocardiography.

DOI: 10.1530/endoabs.37.EP1321

EP1322

Concurrent hyperthyroidism and thyroid cancer – case presentations

Monica Livia Gheorghiu[1,2], Dumitru Ioachim[1], Bogdan Stanescu[1] & Daniel Brasoveanu[1]
[1]C.I. Parhon National Institute of Endocrinology, Bucharest, Romania; [2]C. Davila University of Medicine and Pharmacy, Bucharest, Romania.

Introduction
The coexistence of hyperthyroidism and thyroid cancer is rare (below 2% of cases with hyperthyroidism). If this association predisposes to larger, multifocal or more aggressive cancer (especially in Graves' disease) is a matter of debate. We describe the clinical and hystopathological aspects and evolution in two patients with hyperthyroidism and thyroid cancer.
Patient 1, a 42-year-old woman, was diagnosed in 2008 with Graves' disease (overt hyperthyroidism, mild exophtalmos of the right eye, medium goitre with multiple nodules in the right lobe on ultrasound (1.1–1.7 cm, one 1.5 cm ill-delineated, hypoechoic, with small calcifications). TSH <0.03 mIU/l, high T_3 and T_4). She was treated with methymazole but lost to follow-up for 2 years. In 2011 she presents with overt hyperthyroidism and a large goiter, with a 4 cm 'cold' nodule in the right lobe with microcalcifications and internal vascularisation. She underwent total thyroidectomy and was diagnosed with multifocal papillary carcinoma: 3.3 cm in the right lobe, with capsular invasion, and 1.5 cm in the isthmus ('follicular variant'). No metastases have been detected. The patient has received a total of 150 mCi I131 and is disease-free at 2.5 years of follow-up.
Patient 2, a 56-years-old woman, was diagnosed at the age of 35 with a thyroid nodule and then at the age of 56 with subclinical hyperthyroidism, normal TPOAb and a toxic nodular goitre with a 2 cm nodule with peripheral calcification in the right lobe and a 4 cm 'hot' hypoechoic nodule of in the left lobe. She underwent

total thyroidectomy and was diagnosed with multifocal papillary thyroid carcinoma 'follicular variant': 2 cm in the right lobe, 0.1 cm in the isthmus and 0.2 cm in the left lobe. The large nodule in the left lobe was a follicular adenoma. No local metastases were found. The patient is planned to receive 100 mCi I131.
Conclusion
Although the occurrence of thyroid cancer in hyperthyroid patients is thought to be a rare event, the presence of a suspicious nodule in a hyperfunctioning thyroid should be carefully evaluated to exclude the presence of concurrent malignancy.

DOI: 10.1530/endoabs.37.EP1322

EP1323

Gigantomastia with mastitis during pregnancy in a patient with well controlled thyroid and lupus disease – a case report

Julia Prague, Laura Geddes & Felicity Kaplan
East and North Herts NHS Trust, Hertfordshire, UK.

Introduction
Gigantomastia is a rare condition characterised by excessive benign breast tissue growth that is thought to be a result of elevated physiological levels of circulating hormones (e.g. pregnancy), or an increased sensitivity of the breast tissue to such hormones. Isolated reports describe some medical conditions as precipitants (e.g. systemic lupus erythematosus (SLE)) or drugs (e.g. cyclosporine). Many will proceed to surgical intervention to improve physical and/or psychological suffering.
Case report
A 39-year-old woman of normal weight conceived with *in vitro* fertilisation therapy after a salpingectomy for ectopic pregnancy. She had well controlled Graves' disease and SLE on medication. Shortly after her salpingectomy she noted a gradual increase in her breast size, correlating with her monthly cycle, from a brassiere cup size C to a size E at the time of embryo transplantation. During her pregnancy, her breast size continued to increase at such a rate that her brassiere size changed every 3 weeks. Empiric bromocriptine was started at 30 weeks gestation. At 33 weeks she required inpatient admission for mastitis and a urinary tract infection. At 34 weeks her ultrasound showed oligohydramnios, thought to be secondary to her excessive breast tissue, and so she underwent caesarean section. As she chose not to breastfeed bromocriptine was continued. She had an uneventful postoperative recovery and was discharged three days later. She suffered with two further episodes of mastitis within a month of delivery, and was wearing a size N brassiere that was too small for her. She proceeded to surgery with resection of 6.53 kg of breast tissue; histology confirmed benign proliferative change with no atypia.
Conclusion
Gigantomastia is generally a rare, benign condition but is especially disabling to the pregnant woman. Excellent outcomes are generally achieved with surgery. To our knowledge this is the first documented case in a patient with thyroid disease.

DOI: 10.1530/endoabs.37.EP1323

EP1324

Turner's syndrome associated with idiopathic thrombocytopenic purpura

Zorana Arizanovic[1], Svetlana Vujovic[1,2], Milina Tancic-Gajic[1,2], Miomira Ivovic[1,2], Ljiljana Marina[1], Danijela Lekovic[3], Dragana Rakovic[1] & Dragan Micic[1,2]
[1]Clinic for Endocrinology, Diabetes and Metabolic Disease, Clinical Center Serbia, Belgrade, Serbia; [2]Faculty of Medicine, University of Belgrade, Belgrade, Serbia; [3]Clinic for Hematology, Clinical Center Serbia, Belgrade, Serbia.

Introduction
Turner's syndrome (TS) or Ullrich-Turner's syndrome is genetic condition that affects only females. It is characterized by typical physical features and complete or part absence of one of the X chromosomes. Women with TS have been reported to be at increased risk of autoimmune diseases as compared with other women. Idiopathic thrombocytopenic purpura (ITP), isolated low platelet count (thrombocytopenia) with normal bone marrow and the absence of other causes of thrombocytopenia, is rarely described in patients with TS.
Case report
A 39-year-old female patient was admitted to our Clinic for endocrinological evaluation of primary amenorrhoea. Previously, in October 2012 and June 2013. She was admitted to clinic for haematology due to gingival bleeding, epistaxis and petehial bleeding. Haematological tests confirmed the diagnosis of Idiopathic thrombocytopenic purpura. Endocrinologist was consulted, because of amenorrhoea. Anamnestically, she was hospitalised at the age of 12 because of the short stature and oestrogen replacement therapy was initiated. She used sporadically, without further supervision. Karyotype was not determined. During hospitalisation in our Clinic, on physical examination, her external genitalia appeared as completely normal feminine structures with reduced pubic and axillary hair. Breasts were completely developed with missing nipples. Hormonal analysis showed menopausal values of gonadotropins and oestradiol (FSH = 54.7 IU/l; LH = 21.3 IU/l; E_2 = 29.4 pmol/l; $P < 0.44$ nmol/l; LTH = 515.7 mlU/l; T = 1.2 nmol/l; DHEAS = 2.5 gmol/l; 17 OH-P = 0.19 nmol/l, TSH = 3 mlU/l; fT_4 = 7.7 ng/l; TPO Ab = 32.8 U/ml). Cytogenetic analysis revealed a 45, XO, karyotype, which confirmed the diagnosis of Turner's syndrome. Estroprogesterone therapy was initiated. Regular menstrual bleeding appeared.
Conclusion
Very careful follow up of Turner's syndrome is necessary due to high incidence of cardiovascular diseases, autoimmune diseases and short life expectancy.

DOI: 10.1530/endoabs.37.EP1324

EP1325

Exquisite case of coeliac disease in elderly patient with polyglandular autoimmune syndrome type III; a case report

Natia Katamadze
V.Iverieli Endocrinology, Metabology, Dietology Center 'ENMEDIC', Tbilisi, Georgia.

Introduction
The link between Celiac disease (CD) and type 1 diabetes mellitus is well known. CD is an autoimmune disorder which was considered as a disease of childhood. Now, we know that CD is life-long condition. It affects people of all ages and all body shapes. Screening for CD or type 1 diabetes is recommended in individuals already diagnosed with either disorder. When individuals have both diseases, type 1 diabetes is usually diagnosed first.
Objectives
Our aim is to demonstrate clinical case of CD in 40 years old woman and results of successful treatment of a Polyglandular Autoimmune Syndrome type IIIA (diabetes mellitus type 1, Hashimoto's Thyroiditis and Celiac diasease).
Design and methods
40 years old woman, who has had diabetes mellitus type 1 since the age of 6 years, attended our clinic as her glycemia was poor controlled. She had episodes of severe hypoglycemia and complained of weakness, weight loss, fatigue, diarrhea 4–5 watery stools daily. Laboratory analysis were performed. Thyroid function tests revealed primary hypothyroidism, Hashimoto's Thyroiditis. It was believed that she had chronic diarrhea due to her diabetes and Alpha Lipoic Acid, B vitamins, Actovegin was initiated. After 2 weeks occured swollen abdomen and edema of lower extremities. Abdomen Ultrasound showed rush peristalsis of intestines, no liquid was observed. Biochemical profile was within normal range. CD was suspected as a disease frequently associated with Polyglandular Syndrome Type IIIA. The diagnosis of CD was confirmed by Serologic test for AGA and the biopsy. Gluten free diet was advised. After 2 weeks her diabetes was better controlled. She has had no complaints of diarrhea.
Conclusion
CD screening is recommended in elderly patients with Diabetes Mellitus type 1 as well as in children.

DOI: 10.1530/endoabs.37.EP1325

EP1326

TNF-α and adiponectin pathways are deregulated in endometria from obese women with polycystic ovarian syndrome

Lorena Oróstica[1], Isis Astorga[1], Víctor García[3], Cristian Poblete[1], Carmen Romero[1,2] & Margarita Vega[1,2]
[1]Laboratory of Endocrinology and Reproductive Biology, Faculty of Medicine, University of Chile Clinical Hospital, Santiago, Chile; [2]Department of Obstetrics and Gynecology, Faculty of Medicine, University of Chile Clinical Hospital, Santiago, Chile; [3]Faculty of Health Sciences, University of Antofagasta, Antofagasta, Chile.

Seventy percent of women bearing PCOS are obese; adiponectin and TNFα, as obesity markers, have a dual role in the sensitivity and action of insulin. Adiponectin (insulin sensitising) decreases, whereas, TNFα, IL6 (negative

regulators of insulin pathway) increases in obese-women. Moreover, TNFα decreases the transcript and protein levels of adiponectin. These changes could affect the normal energetic status in endometrium, tissue that exhibits abnormal insulin signalling in the PCOS condition (hyperandrogenic/hyperinsulinic environment). The aim of the present work was to evaluate molecules involved in TNFα (RTNFα 1 y 2, NFkB, p-IKK) and adiponectin (AdipoR1, AdipoR2, APPL1, TAK1, MEK1) signalling in endometria ($n=15$) from lean, Obese and Obese-PCOS women by western-blot, immunohistochemistry and real-time PCR. Also, the number of macrophages was evaluated by CD68 and plasma levels of adiponectin, TNFα and IL-6 were assayed by ELISA. No changes in serum TNF-α levels were observed, however, IL-6 levels increase in both Obese groups vs Lean ($P<0.01$). Adiponectin was lower in Obese-SOP ($P<0.01$). TNFα, its receptors and CD68 levels increase in Obese-PCOS vs other groups ($P<0.05$). Transcripts levels for adiponectin, TNFα/receptors and APPL1 were similar in the three groups of endometria. NFkB nuclear localization was higher in Obese-SOP vs the other groups ($P<0.05$) and activated IKK increased markedly in both groups of Obese vs Lean group ($P<0.0001$). Adiponectin protein levels (plasma and endometrial), AdipoR1, APPL1 and MEK1 were low in Obese-PCOS vs Lean group ($P<0.05$); TAK1 diminished in both Obese endometria ($P<0.05$). Consequently, there is an increased inflammatory environment in endometrium of Obese-PCOS women that could decrease adiponectin signalling, through the participation of TNFα, NFκB activation and/or IL-6 signalling; therefore, affecting insulin signalling under obesity, hyperandrogenic and hyperinsulinic conditions, compromising the energetic metabolism for normal endometrial function.

Disclosure
This study was supported by grants # 1130053 from the Fondo Nacional de Desarrollo Científico y Tecnológico, Chile (to MV) and # 21120541 (to LO) from Comisión Nacional de Investigación Científica y Tecnológica, Chile.

DOI: 10.1530/endoabs.37.EP1326

EP1327

A case of multiple gas-forming pyogenic liver abscesses in diabetic patient

Hyoung Woo Lee, Ho Jin Kim, Jun Ho Lee, Jun Sung Moon, Ji Sung Yoon & Kyu Chang Won
Yeungnam University College of Medicine, Daegu, Republic of Korea.

Background
Gas-forming pyogenic liver abscess is an uncommon, life-threatening infection that is usually found in poorly-controlled diabetic patients. Here, we experienced a case of gas-forming pyogenic liver abscess in diabetes caused by Klebsiella pneumoniae.
Clinical case
A 77-year-old man with 25-year history of diabetes was admitted due to fever for 2 days. On the physical examination, right upper quadrant tenderness of the abdomen was present. Initial laboratory results were: WBC 29 030/mm^3 (Neutrophil 94.3%), C-reactive protein 19.21 mg/dl, Procalcitonin 12.3 ng/ml, BUN/Cr 52.7/2.16 mg/dl, AST/ALT 271/295 IU/l, T-Bil 1.78 mg/dl, serum glucose 448 mg/dl. Abdominal CT showed 1.5–4.4 cm sized multiple gas-forming liver abscesses. Even though culture was negative from drained pus, K.pneumoniae was identified at the blood. The patient was successfully managed with broad-spectrum antibiotics and percutaneous drainage.
Conclusion
The clinical outcome of gas-forming liver abscess appears to be fatal, therefore, an early aggressive therapeutic strategies, such as percutaneous drainage or surgical intervention are needed.

DOI: 10.1530/endoabs.37.EP1327

EP1328

Remission of acanthosis nigricans in a teenager after treatment with metformin

Kyriaki Tsiroukidou[1], Ioanna Zografou[2], Theodora Griva[1], Athena Pyrpasopoulou[1], Maria Papagianni[1], Konstantina Kosta[1], Anastasios Vamvakis[1], Panagiota Karagianni[2] & Christos Sampanis[2]
[1]3rd Pediatric Department Hippokration General Hospital, Thessaloniki, Greece; [2]Diabetes Center Hippokration General Hospital, Thessaloniki, Greece.

Introduction
Acanthosis nigricans is a condition commonly associated with disorders characterised by insulin resistance. Data regarding the treatment of acanthosis nigricans are still insufficient.
Case report
A 10-year-old overweight girl (BMI = 24 kg/m^2) presented at the obesity outpatient clinic. Her family history was negative for metabolic syndrome. Clinical examination revealed extensive acanthosis nigricans involving the neck and armpit. Laboratory tests were normal except for HOMA-IR that confirmed insulin resistance (HOMA-IR = 14). The patient was started on hypocaloric diet and exercise without clinical improvement after 1 year. Acanthosis nigricans expanded involving neck, armpit and thorax, as insulin resistance increased (HOMA-IR = 28.6). Metformin at a dose of 1700 mg daily was added to the diet and exercise with good clinical response. Insulin resistance decreased significantly after 3 months (HOMA-IR = 5.85) and acanthosis nigricans regressed after one year of treatment.
Conclusions
Metformin may be an effective treatment option in some cases of acanthosis nigricans. Larger studies are necessary to establish the efficacy and safety of agents that reduce hyperinsulinaemia and insulin resistance in the treatment of acanthosis nigricans.

DOI: 10.1530/endoabs.37.EP1328

EP1329

Functional analysis of four mutants of the V2 receptor

Beril Erdem[1], Angela Schulz[2], Emel Saglar[1], Torsten Schöneberg[2], Ferhat Deniz[3] & Hatice Mergen[1]
[1]Department of Biology, Faculty of Science, Hacettepe University, Ankara, Turkey; [2]Faculty of Medicine, Institute of Biochemistry, Leipzig University, Leipzig, Saxony; Germany; [3]Department of Endocrinology and Metabolism, GATA Haydarpasa Teaching Hospital, Istanbul, Turkey.

Diabetes insipidus is a disorder characterised by severe liquid-imbalance because of the inability to concentrate urine. Inactivating mutations in either arginine vasopressin receptor type 2 (AVPR2) or aquaporin 2 (AQP2) gene can cause congenital Nephrogenic diabetes insipidus (NDI). AVPR2 is a G protein-coupled receptor (GPCR) and is mainly expressed at the basolateral site of the kidneys collecting duct principal cells. Activation of this receptor by vasopressin is responsible for elevation of cAMP levels resulting in insertion of AQP2 water channels in the cell membrane of the collecting duct cells. In this study, four new mutations of AVPR2 gene (R68W, R67_G69del/G107W, V162A and T273M) were found in patients and were functionally analysed. For this purpose, all mutants were generated by a site-directed mutagenesis strategy. Both, total cellular expression and cell surface expression of mutant receptors were analysed in ELISA experiments. Also, cAMP accumulation and concentration response curves were determined for each mutant receptor. According to total ELISA results, all mutant receptors were synthesised comparable to WT receptor. However, cell surface expression was impaired for all mutants except of V162A. cAMP measurement for mutant and WT receptors revealed reduced Emax values for all mutants. For some mutants (R68W, R67_G69del/G107W and T273M) concentration response curves showed shifted EC50 values to higher vasopressin concentrations. In conclusion, we characterised four new AVPR2 mutations found in Turkish patients. Some mutations lead to shifted EC50 values by only one magnitude and treatment with higher amounts of AVP could be helpful for these patients to reduce high urine volumes and to restore kidney function.

Disclosure
This work was supported by the The Scientific and Technological Research Council of Turkey (Project Number: SBAG 112S513).

DOI: 10.1530/endoabs.37.EP1329

EP1330

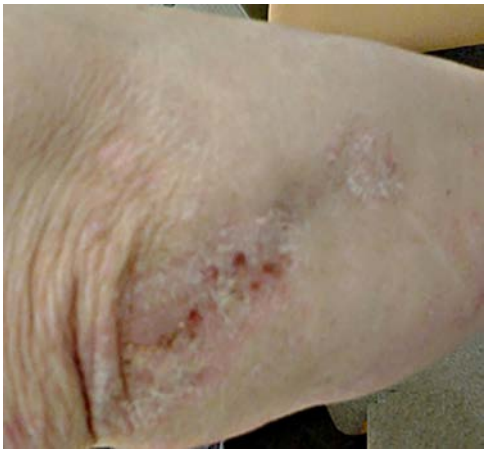
Diabetes, obesity and psoriasis in a 60-year-old woman

José M Varela-Aguilar[1,2], Rosa García-Contreras[1], Ana Calzada-Valle[1], M Luz Calero-Bernal[1], Estefania Pererira-Díaz[1], Fidel Moreno-Verdejo[1], Abelardo Hurtado-Ganoza[1], Francisco Ruiz-Ruiz[1] & Enrique Calderón-Sandubete[1,2]
[1]Internal Medicine Service, Hospital Virgen del Rocío, Seville, Spain; [2]CIBER Epidemiologia y Salud Pública, Seville, Spain.

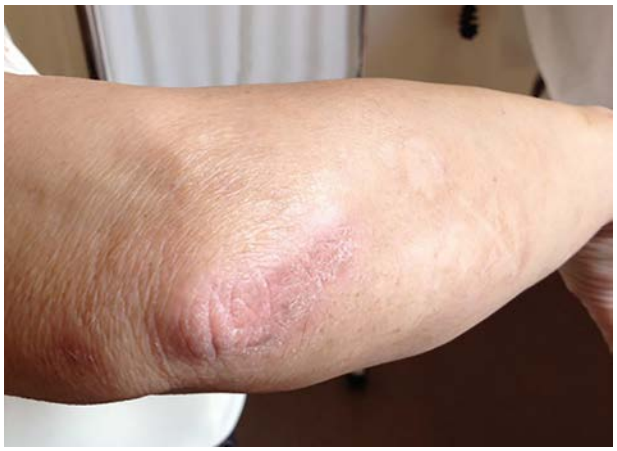
Psoriasis (PS) is a skin disease of immune T-cell mediated. It is well known that obesity is a risk factor for severity PS and PS is associated with the degree of overweight. In addition, patients with PS have increased risk of metabolic disorders such as diabetes mellitus (DM) and dyslipidaemia. All these processes are characterised by the presence of systemic chronic inflammation. Liraglutide, an agonist receptor GLP-1, is being used in the treatment of obesity and diabetes mellitus with excellent results both in glycaemic control and reduced body weight.

Case report

60-year-old woman with a history of type 2 diabetes, type II obesity (78 300 kg; BMI 38.39) and moderate psoriasis which was derived from primary care for poor glycaemic control (glycated Hb: 7.3%). Skin: injuries erythematous scaly plaques on back of hands, elbows, knees, trunk and scalp with PASI 5.8 and BSA 7% (Fig. 1).



Treatment was initiated with metformin 850 mg bid and liraglutide 1.2 mg/s, maintaining the same treatment for psoriasis came performing with topical corticosteroids and methotrexate. Three months after treatment change was revised in consultation objectifying optimal glycaemic control (HbA1c 6.1%), reduction of 8.5 kg in weight and improvement of skin lesions with PASI <3 and BSA 2% (Fig. 2).



Conclusions

The improvement in the weight reduction and improved glycaemic control as well as reduced secretion of proinflammatory cytokines placed the receptor agonists of GLP-1 in a special place for treatment of patients with T2DM and psoriasis. These features, which have yet to be demonstrated on a consolidated basis in clinical practice, can play a key role in the individualization of treatment of patients with T2DM.

DOI: 10.1530/endoabs.37.EP1330

EP1331

Metformin and lactic acidosis: a potentially lethal relationship during intercurrent illness

Marjeta Kermaj[1], Enalda Demaj[1], Gerta Sinani[2], Violeta Hoxha[1], Gerond Husi[1], Armela Cuko[3] & Agron Ylli[1]
[1]University Hospital Center 'Mother Tereza', Tirana, Albania; [2]Hospital Center, Librazhd, Albania; [3]University Hospital Center 'Shefqet Ndroqi', Tirana, Albania.

Introduction

Metformin-associated lactic acidosis (MALA) is defined as a high anion gap metabolic acidosis with high circulating lactate levels and without hypoperfusion. It is associated with a mortality rate up to 50%.The reported frequency is 0.01–0.05/1000 patient-years, mostly in patients with predisposing factors (which affect its clearance or energy metabolism) such as altered renal function, congestive heart, hepatic and respiratory failure, concomitant medications (angiotensin II receptors antagonist), old age. We present a report of a patient with type 2 diabetes who was receiving long term treatment with metformin and developed severe metformin associated lactic acidosis after dehydration, which resulted in renal impairment and consequent accumulation of metformin. We want to remind of a potentially lethal adverse reaction of this drug.

Case report

Our patient was a 64-year-old Albanian woman with a 3 year history of type 2 diabetes mellitus (treated with metformin 850 mg/d) and hypertension (treated with losartan 50 mg/d). She presented to our emergency with acute renal, hepatic, circulatory failure and severe metabolic acidosis, after a week history of abdominal pain, vomiting (associated with poor oral intake) and dyspnoea. Her medication also compromised a 3 day history of clarithromycin for acute sinusitis. She took adequate supportive care, management of concurrent disease, correction of acidemia, acceleration of lactate metabolism, and interruption of the offending drug. Twenty-four hours later, full clinical recovery was observed, with return to a normal serum lactate level.

Conclusions

Our initial impression was that the multiorgan failure was due to a combination of factors, including poor oral intake and nephrotoxic agents. Dehydration in patients taking metformin can lead to MALA. Given that mortality metformin should always be discontinued in such a clinical scenario. This case illustrated the importance of stopping metformin treatment (even small dose) during intercurrent illness, especially dehydration.

DOI: 10.1530/endoabs.37.EP1331

EP1332

Leg oedema: first sign of an ischemic leg which precipitated hyperosmolor hyperglycemic state in a newly diagnosed type 2 diabetes patient

Sushuma Kalidindi, Probal Moulik & Andrew Macleod
Royal Shrewsbury Hospital, Shrewsbury, Shropshire, UK.

Patients with diabetes are prone to peripheral vascular disease. We present the case of an 81 year old female, current smoker who presented to her general practitioner with a 3 day history of ankle oedema for which she received furosemide. She had a background of right above knee amputation due to peripheral vascular disease and essential thrombocythaemia. Five days after commencing furosemide, she developed increased lethargy and confusion. On arrival to hospital, her venous blood glucose was 32.8 mmol/l, ketones of 1.8 mmol/l and she wasn't acidotic. She was dehydrated with sodium of 159 mmol/l, urea of 9.5 mmol/l, creatinine of 43 μ/l. Calculated serum osmolality was 338 mOsmol/kg. Insulin infusion and fluids were commenced. HbA1c was 81 mmol/mol on admission, with no prior history of diabetes. She developed atrial fibrillation while inpatient requiring digoxin. She was found to have a pale, pulseless, cold, ischemic left leg and was considered to be a very high perioperative risk. After discussion with family, she was started on the palliation pathway. This is a rare presentation of acute leg ischemia in a patient with newly diagnosed diabetes. She likely had an ischemic left foot which was masked by leg oedema. Peripheral vascular disease patients, who keep their legs in a dependent position for comfort often present with considerable edema of the feet and ankles. Numerous factors could have contributed to the ischemia, including emboli from atrial fibrillation, essential thrombocythaemia and peripheral vascular disease. Conversely dehydration from HHS could have precipitated her atrial fibrillation.

DOI: 10.1530/endoabs.37.EP1332

EP1333

Potential effects of endocrine disruption: reproductive tract abnormalities in a 4 years boy

Cosmina Rimbu[1], Lisandra Damian[1,2], Ramona Axinte[1], Cristina Preda[1,2], Voichita Mogos[1,2] & Maria Christina Ungureanu[1,2]
[1]Endocrinology Clinic, 'St Spiridon' Emergency Clinical Hospital, Iasi, Romania; [2]'Grigore T. Popa' University of Medicine and Pharmacy, Iasi, Romania.

Endocrine disrupting chemicals are substances, both natural and artificial to which we are all exposed, even in a low dose in our everyday life. Health effects attributed to endocrine disrupting compounds include immune dysfunctions, various cancers, neurological effects and behaviour disorders, reproductive problems, early puberty, etc. Over the past 50 years, an increase in urogenital tract abnormalities in males has been noted. We present a 4 year old boy case report, born at term, by caesarean section, addressed to the Endocrinology Department for micropenis, hypospadias and overweight. His mother was diagnosed with PCOS but she never took anti androgenic treatment before the patient was conceived; she is working in a paint factory. The first consultation revealed: micropenis: 3 cm (−2,5 DS), hypospadias, bilateral descended testicles and normal developed scrotum. Workup: normal pituitary function; DHEAS slightly increased, normal 17OH progesterone; normal abdominal, pelvic and testicular ultrasounds; normal karyotype. We took in consideration next diagnostic assumptions: i) late-onset 3 β-hydroxysteroid dehydrogenase deficiency: excluded – androstendione in limits. ii) 5 α reductase deficiency: hCG stimulation: DHT = 252 pg/ml – borderline values, testosterone/DHT = 12.77 infirm this diagnosis. iii) Androgen partial resistance: the patient has descended testicles; no genetic tests available in our country; good response after androgen treatment iv) Intersexuality due to endocrine disruptors. He received treatment with testosterone enanthate 50 mg at 3 weeks, for 3 months, and his penis increased: 5 cm; is scheduled for hypospadias correction intervention.
Conclusions
Endocrine disruptor pathology must always remain a diagnostic hypothesis in reproductive tract abnormalities in children.

DOI: 10.1530/endoabs.37.EP1333

EP1334

Intentional massive overdose with aspart and glargine insulin: a case report

Daniel-Tudor Cosma[1,3], Alina Silaghi[2,3], Carmen Georgescu[2,3] & Ioan Andrei Veresiu[1,3]
[1]Diabetes, Nutrition and Metabolic diseases Clinical Center, Cluj-Napoca, Cluj, Romania, [2]Endocrinology Clinic, Cluj-Napoca, Cluj, Romania; [3]Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Cluj, Romania.

Intentional insulin overdose in diabetic patients is a rare critical situation. The severity is due to numerous neurological complications, electrolyte disturbances, liver and lung damage or death.
Case report
A 65-year-old male, with significant cardiac and pulmonary pathology, diagnosed with type 2 diabetes since 1996 and treated with glargine (70 U/day) and aspart (68 U/day) insulin is admitted to our centre via ER (emergency room) after an episode of severe hypoglycaemia after administration of 750 U aspart insulin and 280 U glargine insulin. He arrived in the ER 3 h after overdose with a glycaemic value of 47 mg/dl after 40 ml of 33% glucose and 250 ml of 10% glucose. At admission: altered general status, blood glucose 105 mg/dl, tachycardia, multiple injection sites across his abdomen, acanthosis nigricans on the right elbow. Labs exams revealed: hypertrygliceridaemia, hypocalcaemia, slightly elevated creatinine, A1c = 7.9%. An infusion of 20% glucose was begun at 83 ml/h. The glucose infusion rhythm and concentration was adjusted according to the glycaemic profile while maintaining values around 150 mg/dl, with a total duration of infusion of 61 h. Hypocalcaemia was corrected by i.v. administration of calcium gluconate. Electrolytes, phosphorus and magnesium remained within normal limits during hospitalization. Psychological and psychiatric evaluation diagnosed depression and emotional unstable disorder. To increase the insulin clearance i.v. Furosemide was given for 6 days. In the 5th day of hospitalization, we decided the conversion to oral therapy with metformin 2 g/day and sitagliptin 100 mg/day, with a good glycaemic control.
Discussions
Insulin overdose requires intensive and prolonged glycaemic monitoring to prevent recurrent hypoglycaemia due to an early cessation of i.v. therapy. The dose is not correlated with the severity of hypoglycaemia but with a prolonged hypoglycaemic risk higher than that deduced from the pharmacokinetics of insulin analogue administered. This case represents the largest overdose with this analogues treated only by glucose infusion.

DOI: 10.1530/endoabs.37.EP1334

EP1335

Diabetes mellitus associated with optic atrophy, hepatomegaly, hypogonadism

Betul Cavusoglu[1], Suleyman Ahbab[1], Fatih Turker[1], Evrim Cakir[2], Hayriye Esra Ataoglu[1] & Mustafa Yenigun[1]
[1]Haseki Training and Research Hospital Internal Medicine Department, Istanbul, Turkey; [2]Haseki Training and Research Hospital Endocrinology and Metabolic Diseases Department, Istanbul, Turkey.

A 21-year old male with a 4 year history of tip 1 diabetes mellitus was admitted for diabetic ketoasidosis. The patient was on premixed insulin in two divided of 20 units. He had poor control of diabetes with no regular follow up. His height was 141 cm (3rd persentile), and weight was 36 kg (3rd percentile). These anthropometric findings demonstrated low-height for his age. His bone age was consisted with 16 years. Physical examination revealed moon face, hepatomegaly, short stature. The patient was prepubertal with tanner stage 2 for testicular and pubic hair development. Fundus examination revealed bilateral optic atrophy. Laboratory analysis were as following; Hb: 11.3 g/dl (11–16), hct: 37.7% (37–54), AST: 65 U/lt (50) ALT: 61 U/lt (50), urea: 67.5 mg/dl (17–43) creatinine: 0.72 mg/dl (0.67–1.17), C peptide: 0.01 ng/ml, basal serum cortisol: 18.8 µg/dl, FSH: 0.98 mIU/ml (1.37–19.26) LH: 0.98 mIU/ml (1.24–8.62), PRL: 3.18 ng/ml (2.64–13.13), total testesterone: 0.36 pg/ml (1.75–7.81). Ferritin and iron levels were lower for normal limits. His thyroid profile was within normal limits. Somatomedin-C level was 144 ng/ml (84–376). These findings revealed hypogonadotropic hypogonadism. Scrotal sonography was normal. Urine density was 1015 and mean urine volume was 1500 ml. Diabetes insipidus associated with DIDMOAD syndrome was not obtained. Pituitary MR was normal. The coexistence of growth retardation, pubertal delay, hepatomegaly, elevated transaminase levels, diabetes mellitus and optic atrophy has not been reported, yet. It was the first case of the literature.

DOI: 10.1530/endoabs.37.EP1335

EP1336

Severe osteoporosis as a presentation of concealed Swyer syndrome (pure gonadal dysgenesis)

James O'Hare[1] & Kevin Hickey[2]
[1]Department of Endocrinology and Obstetrics and Gynecology, University Hospital Limerick, Limerick, Ireland; [2]Department of Obstetrics and Gynecology, Univesity Hospital Limerick, Limerick, Ireland.

Swyer syndrome (pure gonadal dysgenesis) is characterised by female phenotype with a 46 XY genotype due to a mutation of the sex determining region (SRY) gene on the y chromosome. A 28 year old presented with back pain after an accident and had a 2nd lumbar vertebral fracture and severe osteoporosis. The DEXA scan T score was −4.2. Procollagen Type 1 pro peptide and Osteocalcin levels were high. She had been in good health and denied any family illness. She was 180 cm tall and weighted 63 kg. Breasts were present though not fully developed. She had sparse pubic and axilliary hair. The external genitalia were normal. She had high gonadotropins and low oestrogen and testosterone levels. She had normal serum calcium, phosphate, parathyroid hormone, and vitamin D levels. coeliac and immunoglobulin screen was negative. She had no liver or renal disease. The patient reported menstruating from age 14. Genotype was 46XY -normal male. PCR analysis confirmed the SRY locus on the Y chromosome. MRI and ultrasound of pelvis showed a uterus, fallopian tubes, vagina and one streak gonad. Anti Mullerian factor was low. There is the first reported case of severe osteoporosis as the presentation of Swyer syndrome. It improved with a 29% increase in T score over 2 years with recombinant parathyroid hormone. She menstruated for the first time on cyclical oestrogen. She underwent gonadectomy for the risk of malignancy. Osteoporosis and tall stature were due to life long oestrogen deficiency.The patient later admitted she had concealed primary amenorrhoea for cultural reasons delaying early diagnosis and treatment.

DOI: 10.1530/endoabs.37.EP1336

EP1337

Recurrent severe symptomatic hyponatraemia induced by low-dose oral cyclophosphamide in a patient with ANA-related vasculitis

Rosemary Dineen[1], Agnieszka Pazderska[1], Ronan Mullan[2], James Gibney[1] & Mark Sherlock[1]
[1]Department of Endocrinology, Adelaide and Meath Hospital Incorporating the National Childrens Hospital, Tallaght, Dublin, Ireland; [2]Department of Rheumatology, Adelaide and Meath Hospital Incorporating the National Childrens Hospital, Tallaght, Dublin, Ireland.

Cyclophosphamide is an alkylating agent used in the treatment of malignant and autoimmune diseases. Severe hyponatraemia is a serious electrolyte disorder with life threatening neurological sequelae. We report a case of recurrent severe, symptomatic hyponatraemia that developed in a 61 year old female with systemic vasculitis and Sjogrens syndrome following low-dose cyclophosphamide.
Case report
A 61 year old lady, with ANA positive systemic vasculitis presented for her first cycle of low dose cyclophosphamide (12 mg/kg). She was prehydrated with 1 l of normal saline and drank 3 l of water for prophylaxis of haemorrhagic cystitis. 30 h post treatment her serum sodium fell from 135 mmol/l pre-treatment to 116 mmol/l with decreased GCS, requiring ITU admission. Her urinary sodium was 121 mmol/l, urine osmolality 347 mOsm/kg with a plasma osmolality of 240 mOsm/kg. She received hypertonic saline and recovered without neurological deficits after slow correction over 2 days. Four weeks later, she was admitted to hospital for careful monitoring, at her second cycle, she was again prehydrated. 24 h post treatment her sodium fell to 121 mmol/l with altered consciousness again requiring hypertonic saline. At her third cycle, she was not prehydrated and was commenced on a 1.5 l fluid restriction. Despite fluid restriction, her serum sodium fell from 135 to 129 mmol/l post therapy, without clinical features and corrected spontaneously.
Discussion
Patients receiving cyclophosphamide are at high risk of developing symptomatic hyponatraemia due to SIADH even at low doses of therapy. Cyclophosphamide may induce SIADH, by potentiating the renal actions of AVP. The combination of both increased ADH effect and excess water intake to prevent haemorrhagic cystitis can induce potentially life-threatening hyponatraemia. Clinicians need to be aware of this threat when encouraging large volume prehydration and diuresis with cyclophosphamide therapy. It is possible that pre-hydration with isotonic saline rather than oral water may minimise the incidence of this complication.

DOI: 10.1530/endoabs.37.EP1337

EP1338

Polycystic ovary syndrome in women with type 1 diabetes mellitus: about three cases

Amira Djermane & Samia Ould Kablia
Central Hospital of the Army, Algiers, Algeria.

Introduction
Polycystic ovary syndrome (PCOS) is the most common endocrine disorder and is frequently associated with insulin resistance and type 2 diabetes mellitus. At present, women with type 1 diabetes mellitus (T1DM) are being treated with supraphysiological doses of exogenous insulin with the aim of providing a strict metabolic control. The prevalence of PCOS in women with T1DM varies depending on the diagnostic criteria employed and on the ethnicity of the population studied. In 2000 Escobar-Morreale *et al*., using National Institutes of Health (NIH) 1990 diagnostic criteria, reported a prevalence of 18.8%.
Design
We'll describe three profiles of PCOS in women (age 34, 31, 30 years old) with T1DM that is controlled by high dose of insulin. They have a normal level of SHBG. The PCOS is treated by modification in life style and metformin therapy.
Results
The physiopathology of PCOS in T1DM is unclear. It has been suggested that the use of exogenous insulin at high doses daily to treat T1DM may contribute to the development of PCOS by stimulating the synthesis of ovarian androgens. The normal levels of SHBG in T1DM (insulin concentrations at the portal vein are the main regulators of SHBG) explain both why the most sensitive serum marker of hyperandrogenism here is total testosterone levels, and the milder hyperandrogenic symptoms. The use of metformine permits a significant reduction in the insulin dose administered while providing an improvement in metabolic control.
Conclusions
Every effort must be made for the early detection and treatment of hyperandrogenic disorders in T1DM women because of the large prevalence of PCOS in these women. Future studies should evaluate the consequences of PCOS in women with T1DM and compare the different therapeutic options.

DOI: 10.1530/endoabs.37.EP1338

EP1339

A case of Swyer syndrome with gonadoblastoma and dysgerminoma

Banu Sarer Yurekli[1], Nilufer Ozdemir Kutbay[1], Samim Ozen[2], Emin Karaca[3], Kamuran Acar[4] & Fusun Saygili[1]
[1]Endocrinology Department, Ege University Faculty of Medicine, Izmir, Turkey; [2]Pediatric Endocrinology Department, Ege University Faculty of Medicine, Izmir, Turkey; [3]Medical Genetics Department, Ege University Faculty of Medicine, Izmir, Turkey; [4]Pathology Department, Ege University Faculty of Medicine, Izmir, Turkey.

Aim
The Swyer syndrome belongs to a group of pure gonadal dysgenesis. Karyotype is 46,XY. Aberrations of chromosome Y or SRY gene mutation is present in 15–30% of cases. These patients have high gonadotropin levels and are classified as having hypergonadotropic hypogonadism. The Swyer syndrome in the female requires close followup because of the high risk of neoplastic transformation in the dysgenetic gonads. Herein we report a case of Swyer syndrome with gonadoblastoma and dysgerminoma.
Case
A 22-year-old woman was admitted to the Endocrinology Outpatient Clinic. Menarche age was 15 years old. Breast development was normal during pubertal period without using any oestrogen pill. After 1 year of regular menstrual period, irregular vaginal bleeding occurred. At the age of 18, a big mass was felt on abdomen. She had an abdominal operation for that mass and gonadoblastoma and dysgerminoma were diagnosed pathologically on the right ovary. After that pathologic diagnosis, karyotype study was performed and found as 46,XY. As the integrity of tumour capsule was destroyed, adjuvant chemotherapy was introduced. After chemotherapy, another abdominal operation was performed and gonadoblastoma was diagnosed on the left ovary. There was no laboratory examination regarding to gonadotropin and oestrogen levels before the operations. SRY positivity was present on left oopherectomy material. Phenotypically female paitent with 46, XY karyotype, Swyer syndrome was diagnosed. She was started estrogen/progesterone combination pill.
Discussion
This patient had the normal pubertal development without any delay. Because of this reason, we thought that the gonadoblastoma was hormone active most probably with oestrogen producing one. Unfortunately, we couldn't demonastrate this. Patients with gonadal dysgenesis and 46,XY karyotype should be referred for bilateral gonadectomy because of the high risk of neoplastic transformation. Oestrogen producing gonadoblastoma may mask gonadal dysgenesis and delay the diagnosis of this pathology.

DOI: 10.1530/endoabs.37.EP1339

EP1340

Brown cell tumour from parathyroid carcinoma

Jerome Barrera
Zamboanga City Medical Center, Zamboanga City, The Philippines.

Introduction
Parathyroid carcinoma is a rare cause of hyperparathyroidism. In most cases, hyperparathyroidism is caused by a single benign adenoma. The vast majority of the remaining cases are caused by parathyroid hyperplasia or multiple adenomas. We present here a case of a young Filipina who presented with multiple fractures on all extremities and bilateral parathyroid adenoma.
Case presentation
A 19-year-old Filipina presented with bone pains for 7 months associated with fatigue, anorexia, weight loss and muscle weakness. Subsequently, she had multiple fractures on all extremities and fixed hard masses on the left humerus and tibia. Her past medical and family histories were unremarkable.
Investigations
Corrected calcium was elevated at 15.4 mg/dl, Phosporus was decreased at. Intact PTH (iPTH) was extremely high at 2001 pg/ml (8.5–72.5). X-ray of the

extremities showed osteopenia, endosteal resorptive changes and multiple pathologic fractures. Bone biopsy revealed brown cell tumour/multifocal polyostotic giant cell tumour and negative for malignancy). Ultrasonography of the neck revealed parathyroid adenoma inferiorl of left thyroid gland measuring 2.3×1.1×1.0 cm. Ultrasound-guided FNAB revealed findings consistent with parathyroid carcinoma. She was hydrated and was given diuretic to control the severe hypercalcaemia. She underwent 3½ gland parathyroidectomy with en-bloc left thyroid lobectomy. Intraoperative findings showed a left mass with non well-circumscribed borders invading the capsule and local tissues and a right mass. Serum Calcium and iPTH immediately after OR decreased to 12.8 and 211.8 pg/ml respectively. Further reduction was noted after 24 h of surgery (iPTH, 48 pg/ml; Corrected Calcium: and 9.2 mg/dl).

Discussion/conclusion

Parathyroid carcinoma is a rare malignancy of the parathyroid glands. These tumours usually secrete parathyroid hormone, thereby producing hyperparathyroidism, which is usually severe. Surgery with en-bloc resection is the initial therapy, but when the tumour is no longer amenable to surgical intervention with intent to cure, treatment becomes focused on the control of hypercalcaemia.

DOI: 10.1530/endoabs.37.EP1340

EP1341

An aggressive malignant insulinoma: a case report

Bugra Oztosun[1], Yildiz Okuturlar[1], Meral Gunaldi[2], Ozlem Soyluk[3], Meral Mert[3], Samet Sayilan[1], Mehmet Orman[1] & Ozlem Harmankaya[1]
[1]Department of Internal Medicine, Bakirkoy Dr Sadi Konuk Education and Research Hospital, Istanbul, Turkey; [2]Department of Medical Oncology, Bakirkoy Dr.Sadi Konuk Education and Research Hospital, Istanbul, Turkey; [3]Department of Endocrinology and Metabolism, Bakirkoy Dr Sadi Konuk Education and Research Hospital, Istanbul, Turkey.

Introduction

Insulinomas are rare pancreatic islet cell tumours with an incidence of four cases per million per year. About 10% of all insulinomas are malignant. We here examined an insulinoma with aggressive driving in a young male patient with severe hypoglycaemia in the emergency room.

Case report

34-year-old male patient was admitted to the emergency department with the blurring of consciousness. Blood glucose was 19 mg/dl, consciousness tends to sleep, non-cooperative and disoriented. Continuous dextrose infusion was required and the patient's laboratory tests results: aspartate aminotransferase (AST) 132 U/l, alanine aminotransferase (ALT) 225 U/l, γ glutamyltransferase (GGT) 504 U/l, alkaline phosphatase (ALP) 315 U/l, albumin 3.7 g/dl, total bilirubin 3.3 μg/dl, direct bilirubin 1.9 μg/dl, respectively. When the dextrose infusion interrupted, the blood glucose was 32 mg/dl whereas insulin level was 110 μIU/ml (n=0.1–29.1 μIU/ml) and C-peptide level was 5.6 ng/ml (n=0.9–4.3) respectively. Serum chromogranin A level was 158 ng/l (n: 27–94). Magnetic resonance imaging (MRI) revealed a mass in the pancreatic uncinate process level ~40×41 mm in size. Multiple nodules in different sizes were observed in the left and right lobe of the liver. Biopsy made from fine needle aspiration in pancreatic mass was consistent with neuroendocrine tumours. Tru-cut biopsy made from liver lesions revealed the tumour infiltration. In immunohistochemical studies of tumor, synaptophysin and chromogranin were positive diffuse, KI 67: 7%, CK 7 (+) (weak), CK 20 (−), respectively. Somatostatin receptor type 2 activity in all the liver lobes, multiple lymph nodes and right third rib was detected in Gallium-68 positron emulsion tomography. Metastatic malignant insulinoma was diagnosed with existing findings. In-operable patient, while local and systemic treatment was planning, died because of liver failure.

Conclusion

In the literature a small number of malignant insulinoma patients were treated successfully with different local and systemic treatment. However, we did not have a chance to have local and systemic treatment since the patient died within a month.

DOI: 10.1530/endoabs.37.EP1341

EP1342

VIPoma: an unusual cause of electrolyte disturbance

Diana Boj-Carceller, Diego Álvarez-Ballano, María Eugenia López-Valverde, Leticia Pérez-Fernández, Beatriz Lardíes-Sánchez, Isabel Azcona-Monreal, Alejandro Sanz-Paris & Javier Acha-Pérez
Department of Endocrinology and Nutrition, Hospital Universitario Miguel Servet, Zaragoza, Spain.

Introduction

Vasoactive intestinal peptide-producing tumours (VIPomas) represent a rare type of neuroendocrine tumour whose incidence is 1 in 10 million per year. Most are located in the pancreas. They cause diffuse watery (secretory) diarrhoea, hypokalaemia and achlorhydria and also appear as an uncommon cause of hypercalcaemia.

Case report

A 69-year-old female with previous diagnosis of a 'non-functioning' neuroendocrine pancreatic tumour (2005) with liver metastasis (2009) was admitted for weakness and severe hypokalaemia. She had been admitted for hypercalcaemia a few months before. Her family history was a priori negative for MEN-1 affected. She complained of chronic watery diarrhoea that persisted with fasting (6–10 stools/day) in spite of multiple therapies (surgery, long acting somatostatin analogues, systemic chemotherapy and transarterial hepatic chemoembolization). Analysis showed: impaired fasting glucose (159 mg/dl), hypokalaemia (2.6 mEq/l), metabolic "acidosis" (pH 7.34, serum bicarbonate 15.1 mmol/l), hypophosphatemia (1 mg/dl), hypomagnesemia (1.6 mg/dl) and hypercalcaemia (until 15.3 mg/dl). Serum TSH, calcitonin, cortisol, PRL, glucagon, PTH-rp and 5HIAA were normal. PTH 23.8 pg/ml. 25-0H-vitamin D 35.6 nmol/l. CgA 115 ng/ml. VIP concentrations were high (>116 pmol/l, normal <30 pmol/l). Gastrin 149 pg/ml (13–115). An octreoscan showed known liver disease. There were no bone metastases. Immunohistochemistry was positive for somatostatin, synaptophysin and chromogranin A. Patient needed to be managed with high doses of supplements of potassium, magnesium, phosphorus, periodic i.v. bisphosphonates and a high salt intake. Recently, an essay of cinacalcet was added because of persistent hypercalcaemia.

Discussion

A clinical redefinition of diagnosis was made: VIPoma. Hypercalcaemia might be explained by the stimulatory effect of VIP on bone resorption. However, if normal feedback is intact, PTH concentrations should be low, whereas the patient described had a 'normal' PTH. We have observed a sustained response of calcium levels since cinacalcet introduction. 5% of VIPomas are in context of MEN-1.

DOI: 10.1530/endoabs.37.EP1342

EP1343

Concomitance of pancreatic and neuroendocrine breast tumour – simple coincidence or not?

Iulia Crumpei[1], Alina Fadur[1], Adina Manolachie[1], George Zmau[1], Mihaela Anton[2], Constantin Volovat[3], Maria Christina Ungureanu[1] & Carmen Vulpoi[1]
[1]Depatament of Endocrinology, University of Medicine and Farmacy 'Gr. T. Popa', Iasi, Romania; [2]Departament of Endocrinology, Ragional Hospital, Bacau, Romania; [3]Departament of Oncology, Victoria Hospital, Iasi, Romania.

Introduction

Breast neuroendocrine carcinoma is a rare aggressive neuroendocrine tumour (NET) and the research on this subject is poor. Only seven studies were cited in the literature. Incidence in the population has not been reported, but the prevalence is under 0.1% of all breast carcinomas.

Case report

AV, 72, is hospitalised for bone pain and significant weight loss (15 kg in 2 months). Patient's previous history are: diabetes, hypertension, nodular goitre and suspected pulmonary sarcoidosis in 2011 treated 6 months with corticosteroids. In 2013 abdominal CT revealed in the pancreas an area of 21/20 mm at the isthmus. CA-50 was found negative 14 U/ml (n<25 IU/ml), without any further specific exploration until January 2014 when intense bone pain lead to spinal MRI and bone scintigraphy that objectified secondary dissemination at the lumbar-sacral level and dorsal vertebrae. Abdominal CT reevaluation described: an intraductal pancreatic lesion, secondary disseminations in the liver, spleen and bone. The appearance was suggestive for pancreatic NET, confirmed by high tumoural markers. From the patient's history, we found that she had a left breast fibroadenoma (2013-benign image on mammography). The breast ultrasound identified in the left breast multiple solid nodules with coarse calcifications. Breast cancer markers were increased ACE=31.5 ng/ml (n: 0–1.5), CA 15.3=160 IU/ml (n=0–38.4). A biopsy was performed from the lesion in the liver revealing metastasis of poorly differentiated carcinoma, immunohistochemical data showing carcinoma of the mammary gland with neuroendocrine features. The oncology evaluation staged the tumour in cT2N0M1, ECOG performance status 4 and recommended treatment with Sandostatin LAR, along with initiating treatment with zoledronic acid and aromatase inhibitors.

Conclusions

The peculiarity of the case is the association of a probably pancreatic neuroendocrine tumour with breast carcinoma with neuroendocrine features,

probably evolving for a long time in the past, which was initially considered and treated as sarcoidosis.

DOI: 10.1530/endoabs.37.EP1343

EP1344

Endocrine assays in female patient with relapsing thymus cyst and myasthenia gravis

Mara Carsote[1,2], Dana Terzea[2,3], Ionela Baciu[1,2], Alexandra Mihai[2], Dan Peretianu[4], Florina Vasilescu[3], Mihaela Popescu[2], Raluca Trifanescu[1,2], Anda Dumitrascu[2] & Catalina Poiana[1,2]
[1]C.Davila University of Medicine and Pharmacy, Bucharest, Romania; [2]C.I.Parhon National Institute of Endocrinology, Bucharest, Romania; [3]Monza Oncoteam Hospital, Bucharest, Romania; [4]SCM Povernei Medical Centre, Bucharest, Romania.

Introduction
The congenital cystic neck masses underlie various diagnosis including tymic cysts. Even they are an embryological defects, the adult onset might be seen. The aetiology is not clearly established. The malignant behaviour or infections are correlated to the cysts. Aim: we present a female case with a complicated history of cysts.
Case report
42-year old female is known with the following medical history. Seven years ago she was operated for a pericardia cyst. The computed tomography was normal after surgery until 2014 when she accused breathing difficulties. The computed tomography was performed and a tymic cyst was discovered (of 7 cm). Thoracotomy was chosen as procedure for the cyst: the cyst was partial evacuated during the procedure and then removed but the tymus was conserved. The pathological exam confirmed a simple tymic cyst, with no atipia. After surgery, the patient felt well for about 6 months when she accused again troubles in breathing, and also persistent asthenia. The computed tomography found again the tymic cyst of 4.89 by 4.1 by 6.4 cm, with no other thoracic or cervical anomalies. The patient was referred for an endocrinological check up. The blood pressure was 100 by 65 mmHg. The normal TSH (of 1.5 μUI/ml) was associated with negative thyroid antibodies. The morning plasma cortisol was of 19 μg/dl (normal levels <21 μg/dl). The calcium levels and parathormone, as well as basal plasma metanephrines/normetanephrines were also normal. The prolactin levels were mildly increased (of 28 ng/ml, normal levels <21 ng/ml). The patient was referred to neurological tests and myasthenia gravis was confirmed. A second procedure for the tymus cyst is soon to be done, including the entire organ resection.
Conclusion
The mildly increased prolactin levels are most probably associated to the thoracic surgery. The complete resection of the tymus is encouraged in case of cysts, especially large ones, because of relapse risk.

DOI: 10.1530/endoabs.37.EP1344

EP1345

Oncogenic osteomalacia misdiagnosed as ankylosing spondylitis

Seher Tanrikulu[1], Burak Ince[1], Nurdan Gül[1], Samet Vasfi Kuvat[2], Ayse Kubat Uzum[1], Ferihan Aral[1] & Refik Tanakol[1]
[1]Department of Internal medicine, Division of Endocrinology and Metabolism, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Fatih, Turkey; [2]Istanbul Faculty of medicine, Plastic and Reconstructive Surgery, Istanbul University, Istanbul, Fatih, Turkey.

Oncogenic osteomalacia is a rare paraneoplastic syndrome, which can be associated with phosphaturic mesenchymal tumor or non-mesenchymal tumour. This tumour produces fibroblast growth factor 23 (FGF-23) that leads to subsequent hypophosphataemic osteomalacia. We, hereby present a patient with oncogenic osteomalasia who is misdiagnosed as ankylosing spondylitis. A 54-year old man with weakness, severe arthralgia involving pelvis, hip joints and lower extremities referred to the Rheumatology Department for the treatment of a suspected sero-negative spondiloarthritis and TNF-α inhibitor and glucocorticoid treatment had begun. Despite of 3 years of treatment, there was no relief of symptoms, and laboratory tests had shown hypophosphatemia (0.7 mg/dl) with low vitamin D and normal calcium, PTH levels, referred to Endocrinology clinic. Hypophoshataemia was resistant to oral phosphate replacement. Physical examination revealed a non-tender, mobile, 2 cm nodular lesion at right medial thigh. Magnetic resonance imaging showed an ovular 2.1×1.7 cm hypointense solid lesion with irregular borders in the soft tissue at right thigh. FDG-PET scanning showed high FDG uptake at the lesion, and no other hypermetabolic masses. We performed tumour resection and after an unremarkable post-operative course hypophospatemia resolved within 2 weeks. Histopathological evaluation showed extraosseos giant cell tumour with metaplastic bone cell formation. After surgical removal patient's symptoms have revealed and phosphorous levels became to normal levels. Oncogenic osteomalacia and ankylosing spondylitis, both can present with arthralgia, weakness, difficulty in walking. For the patients who have features suggestive of oncogenic osteomalacia, it is of crucial importance to perform a survey to detect the tumour or tumours responsible.

DOI: 10.1530/endoabs.37.EP1345

EP1346

Stromal tumour revealing a multiple endocrine neoplasia type 1

Ennaifer Houda, Mchirgui Nadia, Ben Abdelghani Khaoula, Khiari Karima & Ben Abdallah Najib
Department of Internal Medicine A – Endocrinology-Charles Nicole University Hospital, Tunis, Tunisia.

Gastrointestinal stromal tumour (GIST) is now defined as a specific, KIT-expressing and KIT-signalling driven mesenchymal tumour of the gastrointestinal (GI) tract. We report a case of stromal tumour revealed by prolonged fever and skin lesions associated with primary hyperparathyroidism and pituitary adenoma.
Observation
We present the case of a 59-year-old patient admitted for prolonged fever with inflammatory syndrome and latte tasks cutaneous lesions. Abdominal ultrasound showed two intra abdominal masses of the left hypochondrium and inter-spleno kidney. Their scanno guided biopsy concluded to a double localisation of a gastro intestinal stromal tumour CKITT^{+}. The dermatological examination found a paraneoplastic dermatosis. The patient was put under Glivec 400 mg/day. A cervicothoracic CT discovered lung nodules. The colonoscopy found a juxta appendiceal tumour with multiple layered flat lesions which the biobsy concludes to a tubulo-villous adenoma with high-grade dysplasia. Hypercalcaemia 2.9 mmol/l is discovered. The diagnosis of primary hyperparathyroidism is confirmed by high PTH 217 pg/ml. A type 1 multiple endocrine neoplasia is evoked. A pituitary MRI found a micro pituitary adenoma. Hormonal exploration has concluded that it was a non-secreting adenoma. An abdominal CT scan finds a nodular hypertrophy of the left adrenal. The dosage of urinary Metanephrine was normal. This case illustrates the possible association of a stromal tumour with MEN1.

DOI: 10.1530/endoabs.37.EP1346

EP1347

Gastrinoma with liver metastasis; is it always a bad news?

Sriranganath Akavarapu, Jayashekara Acharya, Parvathy Valsalakumari & Jeannie Todd
Imperial College NHS trust, London, UK.

Introduction
Gastrinoma is a rare neuroendocrine tumor and associated with liver metastasis in 20–40% of cases. We present a rare case report of a patient with stable liver metastasis due to gastrinoma for more than 35 years.
Case report
A 49 year old male is currently on our regular clinic follow up for the liver metastasis due to gastrinoma. His past history includes open laparotomy and resection of gastrinoma (Proven histologically) at the age of 12. During the surgery liver metastasis was noted. He was followed up in clinic until the age of 20. Later he presented with diarrhoea at the age of 38 and was started on Omeprazole 20 mg TDS. Currently he has no symptoms. Genetic study for MEN-1 syndrome is negative. Blood tests showed raised Gastrin levels of 450 ng/l while on Omeprazole. MRI of abdomen in 2014 showed three large liver lesions with largest lesion size of 7 cm. Gallium Dotate PET scan showed all lesions are metabolically active. Compared to previous CT scan in 2006 and 2010 no change in the liver metastasis size.
Discussion and conclusion
Presence of liver metastasis with gastrinoma generally indicates poor prognosis with some studies suggests 10-year survival rate of only 10–20%. However very indolent gastrinoma with liver metastasis is rare and could be managed conservatively.

DOI: 10.1530/endoabs.37.EP1347

Endocrine nursing

EP1348

Abstract withdrawn.

DOI: 10.1530/endoabs.37.EP1348

EP1349

The effect of self-administration of Ipstyl treatment on patients' lives: a qualitative study of patients with acromegaly

Henriette Brahe Hoei & Jonna Gintberg Jensen
Aarhus University Hospital, Aarhus, Denmark.

In 2014–2015, a study of patients' quality of life after training in self-management of monthly Ipstyl injections is implemented. These injections were previously given by their GPs. Inclusion criteria are described. Sample cuts across gender and age. Ten patients did not respond to mailed offers and 12 did not participate. The reason for this is only known to some of them. Six patients wanting training are invited to an introduction of self-management of Ipstyl and are informed that they can always turn to the department with questions related to self-management. Research interviews were conducted in connection with training. The Data Protection Agency approved the project, and the patients were informed of the rules for participation. An interview guide with validated questions was used, and qualitative interviews have so far been completed by two patients. Interviews of ~40 min were recorded and transcription carried out by the researcher. The patients' statements are categorised and analysed according to Steiner Kvale's analysis model's three operational levels i) the patient's self-understanding, which is a compressed image of the person's perception, ii) critical sense, a broader frame of reference than the patient's own opinion and iii) the theoretical level, providing a framework for interpretation of the meaning of statements (Kvale & Brinkmann 2009: 237ff.). The project's most spectacular preliminary findings are: i) Independence in planning GP consultation; ii) Positive experience of self-management procedure; iii) Self-determination of slow injection rate causing less pain at the injection site. Subsequent initiatives focus on optimising the quality of life of the 22 patients who currently do not want self-management. When they are admitted for their annual check-ups: they will be informed about the project's findings; training does not necessarily mean future self-management; spouses are allowed to participate in the introduction as well as in self-management.

DOI: 10.1530/endoabs.37.EP1349

EP1350

Continuous subcutaneous hydocortisone infusion replacement treatement in adrenal insufficiency – how to start the hydrocortisone infusion

Katerina Simunkova[1], Nevena Jovanovic[2], Espen Rostrup[1], Paal Methlie[2], Marianne Øksnes[1], Roy Miodini Nilsen[4], Hanne Hennø[1], Mira Tilseth[1], Kristin Godang[3], Ana Kovac[1], Kristian Lovas[1] & Eystein Sverre Husebye[1]
[1]Departments of Clinical Science, University of Bergen, Bergen, Norway; [2]Department of Medicine, Haukeland University Hospital, Bergen, Norway; [3]Department of Endocrinology, Oslo University Hospital Rikshospitalet, Oslo, Norway; [4]Global Public Health and Primary Care University of Bergen, Bergen, Norway.

Many patients with primary adrenal insufficiency (Addison's disease) take extra doses of glucocorticoids before or during stressful events, but benefit has not been demonstrated. We aimed to test the effect of an extra dose of glucocorticoids on cardiorespiratory, hormonal and metabolic parameters in response to physical activity in a randomised placebo-controlled, 2-weeks cross-over, clinical trial (clinicaltrials.gov NTC01847690). Ten women with Addison's disease and ten female controls participated in the study. All underwent maximal incremental exercise testing. A stress dose of 10 mg hydrocortisone or placebo was given 1 h before exercise on two occasions. Blood samples were drawn before, and at 0, 15 and 30 min post exercise. The glycaemia was followed by continuous glucose monitoring for 24 h. The primary endpoints were oxygen uptake (O_2 uptake), maximal aerobic capacity (VO_2 max). Secondary outcomes were detailed ergometric parameters, and duration of exercise, post-exercise hypoglycaemic events and glycaemic variability, endocrine and metabolic responses to physical activity, and health status evaluated by questionnaires. VO_2max and duration of exercise were significantly lower in patients compared to controls and did not improve with the treatment. Stress-dosed hydrocortisone elevated serum cortisol significantly ($cortisol_{max}$ mean 671 nmol/l (s.d. 49) vs 204 nmol/l (s.d. 41), $P<0.0001$). After exercise the blood glucose and adrenaline levels were significantly lower, and free fatty acids slightly higher, in the patients than in the controls, irrespective of stress dose. No differences were found between the treatments in metabolic or hormonal parameters or quality of life after the exercise. In conclusion, patients did not obtain benefits from stress-dosed hydrocortisone during strenuous short-term exercise. And such dosing does not seem justified in this setting.

DOI: 10.1530/endoabs.37.EP1350

EP1351

Offspring of nurses working on irregular shifts are more likely to be underweight and less likely to be obese compared with those working on a regular basis

Oya Adsiz Marasuna[2] & Umut Mousa[1]
[1]Department of Endocrinology and Metabolism, B Nalbantoglu Hospital Nicosia, Cyprus; [2]Department of Pediatrics, B Nalbantoglu Hospital, Nicosia, Cyprus.

Introduction
Like many other hospitals nurses work either on irregular shifts or on regular basis in our centre. Also their education levels differ among them. In this study we aimed to analyse some factors which may affect the children of female nurses' adiposity.
Subjects and methods
We included 100 children of female nurses on duty in our hospital. The ages ranged between 2 months and 17 years.
Results
According to standard BMI percentiles, 13 (13%) were underweight, 53 were normal weight (53%), 14 were overweight (14%) and 20 were obese (20%). Fifty seven were the first child (57%), 38 (38%) were the second and 5 (5%) were the third child. Sixty-eight children were born normally and 32 by caesarean section. Mothers of 42 children were working on regular basis compared with 58 working on irregular shifts. Out of the mothers of 13 underweight children 12 were working on irregular shifts and one on regular basis. Similarly out of the mothers of 20 obese children 12 were working on regular basis compared to eight on irregular shifts. These findings were statistically significant ($P=0.016$). Children's adiposity were also positively associated with snack habits ($P=0.003$). There was no association between children's adiposity and mothers' education level, fathers education level, fathers working status, duration of breast feeding, birth weight, children's gender, birth order, time of consumption of additional food and type of birth.
Conclusion
The main finding in our study was that underweight children were from mothers working on irregular shifts and that obese children were from mothers working on a regular basis. This could be attributed to irregular working hours leading to irregular and possibly insufficient family feeding. The mother is generally not with the child at feeding hours. These findings need to be clarified in larger scale studies.

DOI: 10.1530/endoabs.37.EP1351

EP1352

Pegvisomant home care programme leading to rapid IGF1 control likely improves quality of life

Els Rutten, Guy T'Sjoen, Bruno Lapauw, Charlotte Verroken & Els Feyen
Ghent University Hospital, Ghent, Belgium.

Background
Pegvisomant has demonstrated efficacy in attaining IGF1 normalisation in previously uncontrolled acromegalic patients. A home care programme improves treatment compliance.

Aims
Evaluation of home educational program and quality of life (Qol).
Methods
Multicentre observational study involving eight Flemish centres. Uncontrolled acromegalic out-patients were trained for daily subcutaneous pegvisomant injection at home by one specialist nurse during 2 h. Enhanced motivation was provided through regular follow-up visits on day 2, 3 and 7 (60′, and twice 45′, respectively) and 15′ phone calls at month 1, 1.5, 3, 4.5, 6, 12, 18, 24, 30 and 36. Preliminary results include IGF1 at baseline, 3, 4.5, 6, 12 and 18 months. Qol was assessed by Patient-Assessed Acromegaly Symptom Questionnaire (PAQ15).
Results
Eighteen patients were included. Associated treatments were long-acting somatostatin analogues ($n=15$): five patients were treated with octreotide LAR 30 mg monthly, four patients with lanreotide 90 mg monthly and six patients with lanreotide 120 mg monthly. In all participants, IGF1 decreased (sometimes needing dose adjustment of pegvisomant from 10 mg OD to 30 mg OD) and Qol improved significantly over time ($P<0.001$), based on decreased complaints of headache ($P=0.002$), perspiration ($P=0.001$), joint pain ($P=0.007$), fatigue ($P=0.023$) and soft tissue swelling ($P=0.001$). These improvements were durable and no drop-outs were observed Table 1.

Table 1

	Baseline ($n=18$)	3 months ($n=18$)	4.5 months ($n=12$)	6 months ($n=9$)	12 months ($n=11$)
IGF1 (ng/ml) (mean±S.D.)	464±262	221±103	282±236	249±167	217±136
	Baseline ($n=11$)	1 month ($n=18$)	6 months ($n=15$)	12 months ($n=10$)	18 months ($n=9$)
PAQ15 (0–8) (mean±S.D.)	11±7	7±6	6±6	6±5	3±3

Conclusion
Working with a specialist nurse may help to improve Qol by attaining rapid IGF1 normalisation, due to enhancing patients' compliance. PAQ15 score improved both on short and longer term.

DOI: 10.1530/endoabs.37.EP1352

EP1353

Level of knowledge about work accidents and competencies among nursing students

Floreta Kurti[1,2], Vjollca Shpata[1,4], Klodiana Poshi[1,3], Brisilda Refatllari[1], Albana Gjyzari[1,5], Ermira Biu[1] & Tatjana Cina[1]
[1]Faculty of Medical Technical Sciencies, University of Medicine, Tirana, Albania; [2]Service of Gastrohepatology UHC Mother Theresa, Tirana, Albania; [3]Service of Endocrinology UHC Mother Theresa, Tirana, Albania; [4]Intensive Care Unit UHC Mother Theresa, Tirana, Albania; [5]Service of Nefrology UHC Mother Theresa, Tirana, Albania.

Aim
The aim of the study is to identify the current level of knowledge of nursing students at the end of their studies in the Master's degree about competence in general nursing, work accidents and competence of endocrine nurses in diabetes care.
Methods
We had 673 nursing students enrolled in the study. They were all students at the end of their study in the master's degree. 76% of the students were practicing nurses with more than 3 years of work experience. All the students fulfilled a very detailed anonymous questionnaire about work accidents, prevention and post exposure prophylaxis, as well as specific knowledge on tests in relation to normal and abnormal organ function.
Results
We had 108 males (15.7%) and 567 females (84.2%). Mean age of nursing students was 27.38±1.24. Out of 673 students, 580 of them (86.18%) report that they had at least one work accident during their work experience. 102 nursing students (15.15%) had good levels of knowledge about tests in relation to normal and abnormal organ function. Only 38 nursing students (4.75%) had expert level knowledge on the specialised field. Mean years of work experience is significantly higher in nurses with expert level knowledge's, and this is statistically significant, $P<0.05$.
Conclusion
Even after Master studies, the level of knowledge of nurses about prevention of work accidents, post-exposure prophylaxis and competency in special nursing fields is unsatisfactory. These results raise the need for the development of national standards in general nursing and the need for professional accreditation of skills and knowledge into practice. We should focus on work-based and lifelong learning plus supervisionn. Specialist nurses may achieve the expert status, in those competencies relevant to them, after 5 years and more in their specialty.

DOI: 10.1530/endoabs.37.EP1353

Author Index